



Current Perspectives on Umbelliferone: Pharmacological Actions and Future Directions

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ABSTRACT

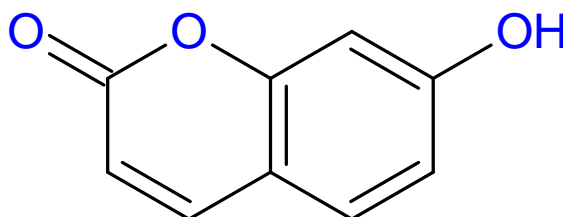
Umbelliferone (UMB) is a naturally occurring 7-hydroxycoumarin belonging to the coumarin family, synthesized and used as a fundamental compound for various coumarin-derived heterocycles. It can be produced through synthetic methods and also bioengineered in *E. coli*. UMB is widely distributed in plants of the Rutaceae and Apiaceae (Umbelliferae) families and extracted using methanol. This review aims to consolidate and provide valuable insights from recent studies on umbelliferone. Pharmacological research has revealed that umbelliferone exhibits diverse effects including anti-diabetic, anti-cancer, anti-infective, anti-rheumatoid arthritis, neuroprotective properties, and the ability to improve liver, kidney, and myocardial tissue damage. Its mechanisms of action involve inhibiting oxidative stress, inflammation, and apoptosis, as well as enhancing insulin resistance, myocardial hypertrophy, and tissue fibrosis. Notably, the inhibition of oxidative stress and inflammation emerges as crucial mechanisms. Overall, these findings underscore umbelliferone's potential therapeutic benefits across various diseases, warranting further research.

Keywords: Umbelliferone, Rutaceae, Apiaceae, Umbelliferae, 7-hydroxycoumarin, Phytochemicals

Introduction

Phytochemicals encompass a diverse group of bioactive compounds sourced from natural origins, particularly plants. Coumarins, characterized by their 2H-1-benzopyran-2-one core, are prevalent in various plants and exhibit a wide array of pharmacological properties. These include anticancer, antimicrobial, antiviral, anticoagulant, antihypertensive, anti-inflammatory, and antioxidant, as well as neuroprotective activities¹.

Umbelliferone (UMB), also known as skimmetine, hydrangine, 7-hydroxycoumarin, and beta-UMB, is a benzopyrone compound (see Figure 1) that naturally occurs within the coumarin family and is widely found in plants. The name "coumarins" originates from 'Coumarou', the common name for the Tonka bean (*Dipteryx odorata* Wild, Fabaceae), from which coumarins were originally isolated².



Umbelliferone
(7-hydroxy-2H-1-benzopyran-2-one)

Figure 1: Structure of umbelliferone

The name UMB is derived from plants belonging to the Umbelliferae family. UMB has demonstrated various pharmacological activities³, including effects on conditions associated with pro-oxidants and reactive oxygen species, such as degenerative diseases, inflammation, tumor cells, and microbial infections.

The potential therapeutic effects of UMB in conditions such as diabetes, cardiovascular and neurodegenerative diseases, inflammatory disorders, various cancer types, and microbial infections (see Figure 1) have sparked increasing interest in developing synthetic derivatives with beneficial pharmacological activities. Moreover, its adaptable structure serves as a scaffold for creating diverse biologically active functionalized 7-hydroxycoumarins^{4,5,6,7}.

Additionally, UMB exhibits no oral toxicity within a dose range of 200 mg/kg^{8,9}, highlighting its potential as a promising platform for developing bioactive compounds based on 7-hydroxycoumarin in drug design.

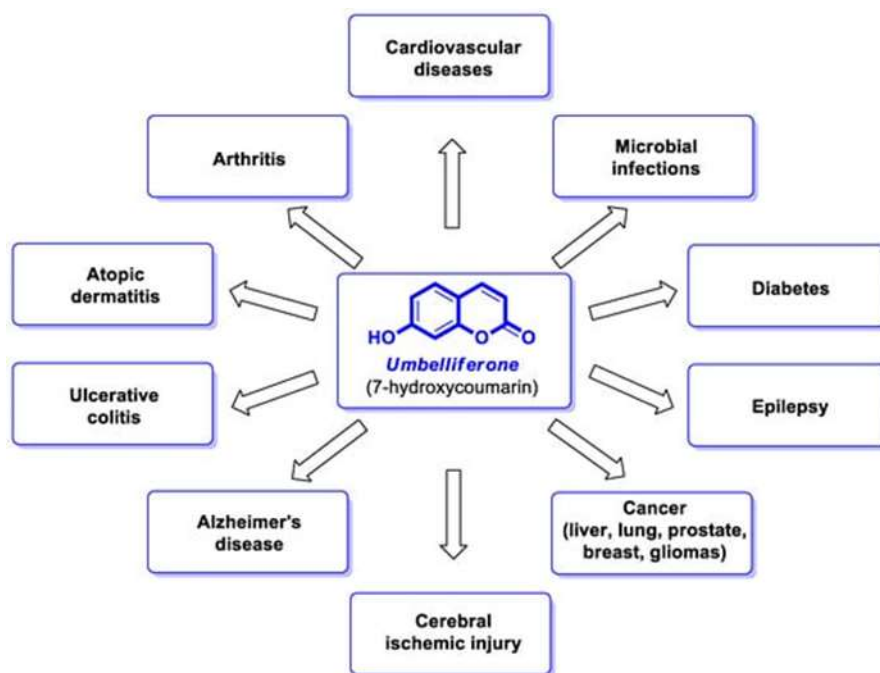


Figure 2: Pharmacological activities of umbelliferone.

Physical Characteristics and Properties

Umbelliferone (UMB) has a molecular formula of C₉H₆O₃. It appears as yellowish-white needle-like crystals with slight solubility in hot water but high solubility in ethanol and dioxane¹⁰. It has a molecular weight of 162.144 g/mol, with a melting point range of 230–233°C and a log P value of 1.58. UMB strongly absorbs ultraviolet light at multiple wavelengths. In acidic conditions, its absorbance maximum is at 325 nm, shifting to 365 nm in alkaline solutions. Fluorescence excitation peaks at 330 nm in acid and 370 nm in alkaline solutions, with emission maxima at 460 nm¹¹.

Infrared (IR) spectra of UMB reveal characteristic bands at 3165 cm⁻¹ (Ar-OH), 1715–1690 cm⁻¹ and 1628–1603 cm⁻¹ (lactone), and 1575 cm⁻¹, 1109 cm⁻¹, and 835 cm⁻¹ (CH). When UMB forms solid interactions with hydroxypropyl- α -cyclodextrin, these IR bands shift to higher wavenumbers^{12,13}.

Sources of Umbelliferone

UMB is widely distributed within the Rutaceae and Apiaceae (Umbelliferae) plant families and is typically extracted using methanol. It is also found in garden angelica, coriander, carrot, and other plants from diverse families (Table 1), such as bigleaf hydrangea (*Hydrangea macrophylla*, Hydrangeaceae, known as hydrangea) and mouse-ear hawkweed (*Hieracium pilosella*, Asteraceae)¹⁴.

Table 1: The plant sources of Umbelliferone.

Plant /extract	Family	Part	Extracting Solvent	Ref.
Acacia nilotica	Mimosaceae	Bark	MeOH	15
Angelica decursiva	Umbelliferae (Apiaceae)	root	MeOH	16
Aegle marmelos	Rutaceae	Fruit pulp	EtOAc	17
Artemisia tridentata	Asteraceae	Whole	MeOH	18
Citrus natsudaiddai	Rutaceae	Whole	Cold Press oil	19
Coriandrum ativum	Umbelliferae	Aerial	MeOH	20
Dystaenia takeshimana	Umbelliferae	Roots	MeOH	21

Edgeworthia chrysantha	Thymelaeaceae	Stem	EtOAc	22
Eriostemon apiculatus	Rutaceae	Aerial	CHCl ₃	23
Ferula communis	Umbelliferae	Peduncles	MeOH	24
Ferula assafoetida	Umbelliferae	Rhizomes	MeOH	25
Fructus Aurantii	Rutaceae	Whole	EtOAc	26
Glycyrrhiza glabra	Fabaceae	Rhizomes	MeOH	27
Haplophyllum villosum	Rutaceae	Aerial/	CHCl ₃	28
Harbouria trachypleura	Umbelliferae	Aerial	MeOH	29
Haplophyllum patavinum	Rutaceae	Aerial & Roots-	MeOH	30

Extraction of Umbelliferone

UMB has been identified in CHCl₃, ethyl acetate, and methanol crude extracts, as well as in the hexane-soluble fraction of methanol extracts. The recommended ratio of plant material (in grams) to solvent volume was 1:15³¹. Effective separations were achieved using high-speed counter-current chromatography with an n-hexane/ethyl acetate/methanol/water solvent system. High pressure liquid chromatography (HPLC) and ultraviolet (UV) analysis at 254 nm detected UMB content in the n-hexane/ethyl acetate fraction separated on an octadecylsilyl C18 column, employing acetonitrile-water gradient elution with a recorded retention time³². The crude extract of UMB from *Chrysantha edgeworthia* was also quantified. HPLC analysis of UMB from *Ipomoea mauritiana* tubers utilized a water-acetonitrile mobile phase on a C-18 reverse phase (RP) column. In high pressure thin layer chromatography (HPTLC), the mobile phase consisted of toluene, isopropanol, and ammonia. Retention times were recorded for HPLC analysis of UMB from grapefruit (*Citrus paradisi*) on a C-18 RP column using a MeOH/H₂O mobile phase³³.

Biosynthesis of UMB:

The biosynthesis of umbelliferone (UMB) coumarins involves several key steps. Initially, cinnamic acid is synthesized from phenylalanine by phenylalanine ammonia lyase (PAL), while para-coumaric acid (p-coumaric acid) is derived from tyrosine using tyrosine ammonia lyase (TAL). Alternatively, p-coumaric acid can be directly derived from cinnamic acid via the P540-dependent enzyme 4-cinnamic acid hydroxylase (C4H). Para-hydroxylation is a prerequisite for ortho-hydroxylation, as confirmed by tracer studies involving *Melilotus officinalis* and *Lavandula angustifolia*, which demonstrated the incorporation of cinnamate into coumarins and 7-hydroxycoumarin³⁴.

The next step involves ortho-hydroxylation of p-coumaric acid to form 2,4-dihydroxycoumaric acid. The trans-double bond in cinnamate is stable and requires isomerization to the unstable cis form before lactonization can occur. Studies have shown that glycoside formation influences trans-cis isomerization. In vitro experiments demonstrated the conversion of trans-diglucoside of 2,4-dihydroxycinnamic acid to cis-diglucoside, and the isolation of skimmian (glucoside of UMB) from *Hydrangea macrophylla* leaf extracts, which hydrolyzes to yield UMB and two glucose molecules. Further studies have implicated CoA-esters in coumarin biosynthesis. 4-coumaroyl-CoA produces UMB utilizing dioxygenase cloned from *Arabidopsis*. Additionally, 4-coumaroyl 2-hydroxylase, identified from *Rutagraveolens*, catalyzes the hydroxylation of active 4-coumaroyl-CoA to produce 2,4-dihydroxycinnamate, which rapidly forms UMB³⁵.

Pharmacological Activities:

Diabetes (Antihyperglycemic Effects):

Post-prandial hyperglycemia is an early indicator of diabetes, and umbelliferone has been reported to exhibit antihyperglycemic effects. In vitro glycation assays have demonstrated its ability to inhibit various stages of protein glycation and effectively inhibit aldose reductase. The ethanol extract of banana flower also shows antihyperglycemic activity through inhibition of the polyol pathway and protein glycation, attributed to umbelliferone. Peroxisome proliferator-activated receptors (PPARs), nuclear fatty acid receptors implicated in metabolic diseases like hyperlipidemia, insulin resistance, and type 2 diabetes, may also play a role³⁶.

Anti-Cancer and Toxicity:

Umbelliferone exhibits anti-carcinogenic properties both alone and in combination with 5-fluorouracil, making it a potential chemotherapeutic agent against colon carcinogenesis induced by 1,2-dimethylhydrazine. It also mitigates the side effects of 5-fluorouracil. Studies have shown anti-cancer activity against laryngeal cancer cells and liver hepatocellular cell lines, inducing apoptosis, cell cycle arrest, and DNA fragmentation^{37,38}.

Neuroprotective activity:

UMB has shown potential protective effects in neurodegenerative diseases³⁹. Studies have indicated its neuroprotective properties in various animal models, including a chronic, unpredictable, mild-stress-induced rat model of depression, a rat model of focal cerebral ischemia-reperfusion, and a mouse model of Parkinson's disease. Additionally, UMB exhibits procognitive effects in rats with STZ-induced cognitive dysfunction, potentially through mechanisms that include inhibiting acetylcholinesterase and reducing oxidative stress, neuroinflammation, and neuronal loss⁴⁰.

Molluscicidal Activity:

Umbelliferone demonstrates larvicidal activity against *Fasciola gigantica* larvae, both in vivo and in vitro, with efficacy dependent on time and concentration. Factors such as high temperature, low pH, and increased free carbon dioxide enhance larval mortality, whereas dissolved oxygen in winter reduces mortality. Formulations combining umbelliferone with attractant amino acids show promise in molluscicidal applications⁴¹.

Anti-Inflammatory:

Derived from *Saussurea laniceps* along with scopoletin, umbelliferone is recognized as a major anti-rheumatic component combating rheumatoid arthritis. It acts through a multitarget mechanism, inhibiting tyrosine kinases on fibroblast-like synoviocytes, thereby blocking their proliferation, migration, and invasion. This action also disrupts NF- κ B signaling, a key mediator of inflammatory cascades, suggesting potential for developing multitarget anti-rheumatic drugs⁴².

Antiepileptic Agents:

Umbelliferone derivatives, particularly those involving a morpholine-acetamide group at position C-7, exhibit antiepileptic effects possibly through synergistic interaction with γ -aminobutyric acid ionotropic receptors (GABAA). These derivatives have shown significant antiepileptic activity comparable to valproic acid, indicating potential in epilepsy treatment⁴².

Fluorescent Probe:

Its fluorescent properties have been utilized to develop a hydrogen peroxide-specific fluorescent probe, demonstrating selectivity over other reactive oxygen species⁴³.

Traditional Uses:

Medicinally, umbelliferone is used for its anti-inflammatory, antioxidant, antifungal, and anticancer properties. It is also incorporated into sunscreen formulations to protect against UV radiation damage and utilized in traditional perfumery and flavoring industries. Additionally, it serves as an insect repellent and finds application as a dye in traditional textile industries for coloring fabrics and fibers⁴⁴.

Conclusion:

Umbelliferone, or 7-hydroxycoumarin, is a natural compound belonging to the coumarin family. It serves as a foundational molecule for synthesizing a diverse array of coumarin-heterocycles. UMB is found widely across plant families such as Rutaceae and Apiaceae (Umbelliferae), and others, and is extracted using methanol. Known for its antibacterial and antifungal properties, UMB is utilized in the treatment of diabetes, demonstrated in studies using extracts from *Aegle marmelos* Correa that reduce blood glucose levels. It also shows promise in cancer treatment, particularly against hepatocellular carcinoma using extracts from *Ferula communis* against the HepG2 HCC cell line. UMB exhibits antioxidant effects and is used in treating conditions like cerebral ischemia and Parkinson's disease, where it inhibits MPTP-induced dopaminergic neurotoxicity, restores GSH levels, and prevents apoptosis. Additionally, UMB is applied in the treatment of bronchial asthma. It is incorporated into biodegradable polymers to form Solid Lipid Nanoparticles (SLNs) using tween60 & tween20, and into phytosomes via solvent evaporation techniques, facilitating efficient drug delivery. UMB also shows potential in mitigating the adverse effects of anti-inflammatory agents. However, given the complexity of diseases, further exploration of other mechanisms of action beyond antioxidant and anti-inflammatory effects is warranted. Moreover, clinical trials are essential to validate the pharmacological effects of umbelliferone observed in experimental research.

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