Bulletin of Faculty of Pharmacy, Cairo University xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Bulletin of Faculty of Pharmacy, Cairo University

journal homepage: www.sciencedirect.com

Review Paper

# Umbelliferone: Sources, chemistry and bioactivities review

Ofentse Mazimba

*Botswana International University of Science and Technology, Palapye, Botswana*

ARTICLE INFO

*Article history:*
Received 16 March 2017
Received in revised form 2 May 2017
Accepted 10 May 2017
Available online xxxx

*Keywords:*
Umbelliferone
Anti-bacterial
Anti-tumor
Cytotoxicity
Synthesis
Biosynthesis

ABSTRACT

Umbelliferone is a 7-hydroxycoumarin that is a pharmacologically active agent. It is widely distributed within the Rutaceae and Apiaceae (Umbelliferae) families and is efficiently extracted using methanol. Umbelliferone is a fluorescing compound used as a sunscreen agent. It is synthesized using the Pechmann condensation reaction of resorcinol and formyl acetic acid. Biosynthetically it is synthesized using the phenylpropanoid pathway. Umbelliferone is a synthon for other coumarins and heterocycles with improved biological activities. In the Literature modest antibacterial and antifungal activities are reported with MIC values of 500–1000 μg/mL, but exhibited good *E. coli* anti-biofilm formation. Umbelliferone shows good inhibitions of DPPH, hydroxyl, superoxide anion and ABTS radicals. Other reported activities are anti-inflammatory, anti-hyperglycaemic, molluscicidal and anti-tumor activities.


**Contents**



*Abbreviations:* UMB, Umbelliferone; EI-MS, Electron Impact Mass Spectrometry; NMR, Nuclear Magnetic Resonance; UV/Vis, Ultraviolet–Visible; HPLC-UV, High Performance Liquid Chromatography Coupled to Ultraviolet Detector; HP-TLC, High Performance Thin Layer Chromatography; $R_f$, retention factor; PAL, phenylalanine ammonia lyase; TAL, tyrosine amino lyase; C4H, 4-cinnamic acid hydroxylase; DGC, diglucoside of 2,4-dihydroxycinnamic acid; CoA, coenzyme A; F6′H, feruloyl CoA-6′ hydroxylase; U6P, Umbelliferone 6-prenyltransferase; GGT, gamma glutamyl transferase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; AChe, acetylcholinesterase; CFU, Colony Forming Unit; DPPH, 2, 2-diphenyl-1-picrylhydrazyl; $ABTS^{\cdot+}$, 2,2-azino-bis-3-ethylbenzothiazoline-6-sulphonic acid radical cation; NADH, nicotinamide adenine dinucleotide; $IC_{50}$, 50% inhibitory concentration; $LC_{50}$, 50% lethal concentration; $EC_{50}$, 50% effective concentration; MIC, minimum inhibitory concentration; MRSA, methicillin resistant *Staphylococcus aureus*; ARP, antiradical power; MTT, 3-(4,5-Dimethyl thiazol-2-yl)-5-diphenyl Tetrazolium Bromide; AAPH, 2,2′-azobis(2-amidinopropane) dihydrochloride; TBA, thiobarbituric acid; DNA, deoxyribonucleic acid; COX, cyclooxygenase; HFD, high fructose diet; STZ, streptozotocin; HCC, hepatocellular carcinoma; A-549, Human Small Lung Carcinoma; HT-29, Human Colon Carcinoma; Hela, Human Cervical Carcinoma; RPMI, Human Nasal Septum Carcinoma; Hep G2, Human Liver Carcinoma.

Peer review under responsibility of Faculty of Pharmacy, Cairo University.

*E-mail address:* mazimbao@biust.ac.bw

http://dx.doi.org/10.1016/j.bfopcu.2017.05.001
1110-0931/

Please cite this article in press as: O. Mazimba, Umbelliferone: Sources, chemistry and bioactivities review, Bulletin Facult Pharmacy Cairo Univ (2017), http://dx.doi.org/10.1016/j.bfopcu.2017.05.001

## 1. Introduction

Umbelliferone is a coumarin widely spread in plants and is a benzopyrone in nature. The coumarin name originates from 'Coumarou', the vernacular name for the tonka bean (*Dipteryx odorata* Willd, Fabaceae), from which coumarins were isolated in 1820 [1]. The umbelliferae family is inclusive of economically important herbs such as sanicle, alexanders, angelica, asafoetica, celery, cumin, fennel, parsley and giant hogweed. The name Umbelliferone on the other hand was derived from the umbelliferae family of plants, and the latter were named for their umbrella-shaped inflorescences [1,2]. The main feature for Apiaceae (Umbelliferae) is the inflorescence gathered within the compound umbels, a parasol-like inflorescence. The plant-derived phenolic coumarins have been purported to play a role as dietary antioxidants because of their consumption in the human diet in fruits and vegetables, while umbelliferone (UMB) has also been reported to have antioxidant properties [3] UMB is used as a sunscreen agent and optical brightener in textiles [4,5]. UMB is a 7-hydroxycoumarin that is a pharmacologically active agent. By virtue of its structural simplicity UMB has been generally accepted as the parent compound for the more complex coumarins and is widely used as a synthon for a wider variety of coumarin-heterocycles [6,7].

In light of the considerable importance of umbelliferone (UMB) in synthesis and its pharmacological properties, this review was undertaken in an effort to summarize the available literature about this bioactive natural product and its analogues. The review will detail the recent studies on the chemistry and bioactivity of UMB. The paper present the occurrence, isolation, characterization and application of UMB in synthetic operations. The biological properties associated with UMB and its analogues with a focus on their potential antioxidant applications are also examined.

## 2. Isolation and sources of UMB

### 2.1. Physical characteristics

Umbelliferone yellowish-white crystals are slightly soluble in hot water, but have good solubility in ethanol [8]. UMB molecular formula is $C_9H_6O_3$ and the needle crystals recrystallized from chloroform melts at 224–227 °C [9,10]. The dimensions of a single crystal grown by the cryostat process are 5.4 mm × 4.2 mm × 1.85 mm [11]. The optimized geometry is planar and the OH group lies on the same plane as the whole molecule [12].

The IR spectra of UMB shows bands at 3165 (Ar-OH), 1715–1690 and 1628–1603 (lactone), 1575, 1109 (C=C) and 835 (CH) $cm^{-1}$. When UMB form strong interactions with hydroxypropyl-α -cyclodextrin the IR bands shift to higher wavenumbers [13–15]. The UV spectra (MeOH) $\lambda_{nm}$ (log $\varepsilon$) shows maxima's at 339 (0.50), 294 (0.36), 242 (0.77) nm [14]. The absorbance maxima in acid is 325 nm while in alkaline solution it shift to 365 nm. The fluorescence excitation maxima in acid and alkali solutions are 330 and 370 nm respectively, while the emission maxima is 460 nm [16]. Another report states that umbelliferone shows blue emission band at $\lambda_{max}$ = 460–480 nm [17] and a positive test with $FeCl_3$ indicated by the deep blue colour [18]. The typical umbelliferone bright blue spot under UV/Vis $R_f$ values reported for authentic and isolated samples [19–22] are shown in Table 1.

The NMR data for umbelliferone is shown in Table 2 and its chemical structure is shown in Fig. 1 [9,13,14,23].

The EI-MS (rel. intensity) spectra showed peaks at *m*/*z* 162 $[M]^+$ (77), 134 (100), 106 (28), 105 (24) and 78 (30) [13,14,23]. The fragmentation pattern features the loss of one molecule of carbon monoxide leading to the peak at *m*/*z* = 134 followed by a loss of a second molecule of CO or a formyl radical (CHO) giving the peaks at *m*/*z* = 106 and 105 respectively [20,24].

### 2.2. Sources and extraction

Umbelliferone has been reported from the $CHCl_3$, ethyl acetate and methanol crude extracts and the hexane soluble fraction of the methanol extract. Silica gel column chromatography eluted with *n*-hexane and ethyl acetate or $CHCl_3$/MeOH solvent mixtures of increasing polarity were employed for the fractionation and isolations. The extraction efficiency of MeOH was reported to increase when the MeOH concentration increased from 10 to 80%, extracting increasing amounts of coumarin, 1.5–1.8 g/100 g dry extract (25 °C), which dropped to 0.6 g/100 g dry extract at 100% MeOH. The optimal ratio of plant matter (in grams) to solvent volume was 1:15, which had 1.7 g/ 100 g dry extract UMB content [25].

Successful separations were reported using high speed counter current chromatography solvent system *n*-hexane/ethyl acetate/methanol/water (4:6:4:6, v/v) with a partition coefficient (K) value of 0.64 [23]. The HPLC-UV (254 nm) analysis of umbelliferone content in *n*-hexane/ethyl acetate (6:4 *v*/*v*) fraction from the ethyl acetate extract on ODS C18 column using acetonitrile-water linear gradient elution at 0.6 mL/min the retention time was reported to be 10 min. The *Edgeworthia chrysantha* umbelliferone crude extract content was 6.89% [23]. Umbelliferone from the tubers of *Ipomoea*

**Table 1**
TLC chromatogram $R_f$ values using different solvent mixtures.

| Solvent | Ratio *v*/*v* | $R_f$ |
|---|---|---|
| Chloroform /methanol | 97:3 | 0.74 |
| | 9:1 | 0.35 |
| Chloroform/formamide | 1:1 | 0.43 |
| Benzene/acetone | 9:1 | 0.39 |
| Benzene/chloroform | 1:1 | 0.04 |
| Toluene, ethylformate/formic acid | 5:4:1 | 0.59 |
| Toluene:ethyl acetate, 1:1 | 1:1 | 0.50 |
| Toluene/chloroform/acetone | 8:5:7 | 0.67 |
| Toluene/chloroform/acetone/acetic acid | 8:5:7:0.4 | 0.67 |

Data Refs. [19–22].

**Table 2**
NMR data for umbelliferone in $CDCl_3$ and $[CD_3OD]$.

| Position | $^1H$ (400 MHz) $\delta_H$ | $^{13}C$ (100 MHz) $\delta_C$ |
|---|---|---|
| 2 | | 160.5 [162.6] |
| 3 | 6.16 (1H, *d*, *J* = 10.0 Hz) [6.19 (1H, d, *J* = 9.5 Hz)] | 112.0 [112.8] |
| 4 | 7.87 (1H, *d*, *J* = 9.1 Hz) [7.86 (1H, d, *J* = 9.5 Hz)] | 144.2 [144.5] |
| 4a | | 111.9 [111.9] |
| 5 | 7.50 (1H, *d*, *J* = 9.1 Hz) [7.46 (1H, d, *J* = 8.5 Hz)] | 129.7 [129.3] |
| 6 | 6.83 (1H, *dd*, *J* = 2.7 Hz, 8.2 Hz) [6.87 (1H, dd, *J* = 8.5, 2.3 Hz)] | 113.2 [113.7] |
| 7 | | 161.6 [161.4] |
| 8 | 6.74 (1H, *d*, *J* = 2.7 Hz) [6.78 (1H, d, *J* = 2.3 Hz] | 102.5 [103.0] |
| 8a | | 156.2 [155.9] |

Data Refs. [9,13,14,23].

Please cite this article in press as: O. Mazimba, Umbelliferone: Sources, chemistry and bioactivities review, Bulletin Facult Pharmacy Cairo Univ (2017), http://dx.doi.org/10.1016/j.bfopcu.2017.05.001