Coumarin-based products: Their biodiversity and pharmacology

Reem N. Ismael1, Yasser F. Mustafa1*, and Harith K. Al-Qazaz2

1 Department of Pharmaceutical Chemistry, College of Pharmacy, University of Mosul, Mosul, Iraq.
2 Department of Clinical Pharmacy, College of Pharmacy, University of Mosul, Mosul, Iraq.
Corresponding author: Dr.yassermustafa@uomosul.edu.iq

Received 05-11-2021 Accepted 08-12-2021

ABSTRACT

Background: The plant kingdom generates and releases a wide range of secondary-metabolites, which have several effects on biological, toxicological, and ecological systems that may act in a similar manner to chemically synthesized compounds. One of these secondary-metabolites are coumarins, which are obtained from many plants, fungi, and bacteria. Coumarins are well-known due to their anticancer, antiviral, antifungal, and antibacterial properties. This study aims to provide a short overview of the biodiversity and pharmacological applications of coumarins, and its natural congeners, as well as an assessment of future medicinal benefits. Also, the study extended to review some of the data related coumarins and their derivatives, particularly those related to pharmaceutical and biological actions.

Conclusion: The implications of coumarins on the health of humans is a multifaceted issue, with many concerns about their safety, toxicity, and medicinal merits. Based on the findings of this review, the authors suggested that different bioactive coumarins for treating a variety of chronic health conditions, including cancer, Alzheimer's disease, HIV, diabetes, and hypertension.

Keywords: Natural Coumarins, Biomedical activities, Secondary-metabolites, Antihypertensive, Anti-inflammatory.

INTRODUCTION

Secondary-metabolites are compounds produced and released by plants that serve a range of functions, including defense against insects, pests, fungi, bacteria, predators, and weeds, in addition to being toxic to herbivores.1,2 Several of these compounds are used as guide molecules in the development of herbicides and pesticides to protect plants from these
noxious agents. Some of secondary-metabolites having toxicological and ecological properties are similar to those detected in the artificial pesticides.

Plants use a variety of mechanisms to release secondary substances into their biochemical milieu, including foliate and bark disintegration and volatile emissions. As a result, they have an impact on the absorption of vital plant nutrients and act as natural poisons because they may alter the chemistry of the rhizosphere. Although secondary-metabolites have diverse phytochemical properties, they also provide a potential ecological role in safeguarding the environment.

Plants' biological reactions to various secondary-metabolites are complicated; rather than being simple adapting processes to different types of biotic stress. These echoes may result from creating many different forms of ecological communication and interactions.

There are hundreds of different phyto-metabolites with a broad spectrum of activity; these chemicals can affect plant growth and productivity through various biological processes. Biological and ecological research has focused on gathering information on the interactions between various environmental agents and plants by qualitative and quantitative evaluating of various secondary-metabolites.

Different vegetations, including grasses, grains, and medicinal plants, have shown varying amounts of coumarins. Coumarins production occurs within fruits in the first degree but also in other plant parts, such as stems, leaves, and roots. The importance of various coumarins has been reported by many investigators, and the research evaluating clastogenic and phytochemical behavior has proved the phytochemical activity of these compounds. However, the toxic effects of many coumarin and coumarin-related products remain unknown, raising concerns about their safety in medicinal treatments and dietary intake.

The benefits of coumarins exposure on people's health are complicated, and many concerns about their medical therapeutic value, pharmacology, and dietary intake remain unanswered. The purpose of this article is to summarize what is presently known in the literature on the biodiversity and pharmacology of the coumarin family, including the plant sources of coumarins and the therapeutic health effects resulting from coumarins' exposure.

**Spreading of coumarins throughout vegetative parts** Several natural products and plant-based bioactive compounds have shown exceptional therapeutic effectiveness against human infections and metabolic diseases. Many of the significant therapeutic plants which contain coumarins are displayed in Figure 1. Many furanocoumarins were identified in the products isolated from the leaves and fruits of the plants commonly known as *Angelica archangelica* and *Pastinaca sativa* respectively.
Coumarins levels in several plants have been measured and vary from 0.001 g per kg in celery to 7g per kg in cinnamon, and up to 87 g per kg in cassia\textsuperscript{15}. Also, it is observed that cassia powder contains 1.5 g per kg of coumarins, while in cassia sticks, the value is less than 1g per kg\textsuperscript{16}. Coumarins of \textit{Dipteryx odorata}, \textit{Cinnamomum cassica}, and \textit{Anthoxanthum odoratum} can act as natural tasting and aromatic ingredients\textsuperscript{17}. \textit{Bilberries}, \textit{cloudberry}, \textit{chicory} and \textit{green tea} are also rich in various types of coumarins\textsuperscript{15}.

Coumarins from \textit{Pastinaca sativa} have been shown to collect greater in seed coats and fruit oil tubes than in other plant parts\textsuperscript{13}. According to recent studies, the amounts of coumarins are also varied in different parts of the plants depending on the stage of development. In many plant species, such as \textit{Apium graveolens}, \textit{Pimpinella anisum}, \textit{Pastinaca sativa}, \textit{Psoralea bituminosa}, \textit{Heracleum lanatum}, and \textit{Ferula communis}, it was observed that the concentrations of coumarins are higher in the premature leaves compared to their corresponding amounts in mature leaves\textsuperscript{13,18}.

Bergapten levels are differ from the leaf to the petiole in \textit{Apium graveolens}, furthermore, the bergapten concentrations increase throughout the seedling stage and decrease at maturity, demonstrating a seasonal pattern\textsuperscript{19}. Also, furanocoumarin-specific bergaptol-O-methyltransferases may be only found in older parsley leaves\textsuperscript{20}.

Aflatoxin B1, a natural occurring coumarin derivative, is the most often found in \textit{Aspergillus species}. It is worth mentioning...
that Aflatoxin B1 is a fungal metabolite that has the potential to be carcinogenic21.

Coumermycin A1 and Chlorobiocin have a 3-amino-4-hydroxy-coumarin moiety and may be produced from several Streptomyces types22. Besides, several coumarin-based products were isolated from celery (Apium graveolens L. var. dulce Miller) leaves23, while furanocoumarins are found only in schizogenous canals of this plant seeds24. In cow parsnip, Heracleum lanatum Michx, furanocoumarins have concentrated predominantly in the petiolar and foliar canals in comparison to the laboratory or glasshouse yields23. In Table 1, various categories of coumarin-based products with their properties and examples are listed.

**Table 1: List of various categories of coumarin-based products with their characteristics and examples**

<table>
<thead>
<tr>
<th>Categories</th>
<th>Characteristics</th>
<th>Example(s)</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple coumarins</td>
<td>The benzene component of coumarin nucleus has been hydroxylated, alkoxyalted, or even alkylated.</td>
<td>Scopoletin (7-hydroxy-5-methoxycoumarim).</td>
<td><img src="image" alt="Structure" /></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Umbelliferone (7-hydroxycoumarin).</td>
<td><img src="image" alt="Structure" /></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Scopolin (7-(β-D-Glucopyranosyloxy)-6-methoxy-2H-1-benzopyran-2-one).</td>
<td><img src="image" alt="Structure" /></td>
</tr>
<tr>
<td>Pyrano-coumarins</td>
<td>Pyran ring is directly fused with the benzene component of coumarin nucleus.</td>
<td>Seselin (8,8-dimethylpyrano(2,3-f) chromen-2-one).</td>
<td><img src="image" alt="Structure" /></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Xanthyletin (2,2-dimethylpyrano(3,2-g) chromen-8-one).</td>
<td><img src="image" alt="Structure" /></td>
</tr>
</tbody>
</table>
Abiotic environmental variables, such as seasonality, salinity, dryness, osmotic stress, soil minerals, and light intensity can impact the production of secondary metabolites and their storage in plants\textsuperscript{1,2,25}. Indeed, abiotic environmental variables that limit the synthesis of secondary metabolites indirectly influence the plant-biotic interactions\textsuperscript{1}.

Sunflowers contain different types of phytoalexins like scopoletin and ayapin\textsuperscript{26}. Scopoletin can be detected in the leaf leachates, while ayapin can be isolated from broomrape-infected sunflowers plants\textsuperscript{3}.

---

**Abiotic variables that influence coumarins content in plants**

**Biological potentials of coumarins and their medicinal values**

Natural coumarin compounds are phytochemicals with antiviral, antimicrobial, and other biological and medicinal effects\textsuperscript{27}. Moreover, some of these naturally occurring products may possess anti-hypertensive\textsuperscript{28}, anti-parasitic, anti-oxidant, anti-proliferative, anti-worms, and anti-inflammatory properties\textsuperscript{29–31}.

**Coumarins-effectiveness against inflammation**

Inflammation involves creation and release of numerous mediators such as bradykinins, histamines, prostaglandins, and serotonin caused by a response to the chemical,
physical, or biological stimulation of cells\textsuperscript{32}. According to some authors, the production of reactive oxygen species (ROS) and harmful free radicals contributed to the formation of severe chronic illnesses, such as tissue edema and inflammation. Different coumarin-based products have anti-inflammatory activity through their scavenging ability towards these dangerous molecules\textsuperscript{33}.

Numerous coumarin compounds, as reported in Table 2, have been found to have anti-inflammatory properties, including umbelliferone, scopoletin, visniadin, bergapten, fraxetin, and marmin\textsuperscript{34}. Besides, umbelliprenin had been found to have \textit{in vitro} anti-inflammatory action based on its capability to diminish the carrageenin-promoted paw edema by about 39\% percent\textsuperscript{35}.

Table 2: Some coumarin derivatives with anti-inflammatory properties and their chemical structures.

<table>
<thead>
<tr>
<th>Code</th>
<th>Compounds name</th>
<th>Chemical structure</th>
<th>Code</th>
<th>Compounds name</th>
<th>Chemical structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>RN1</td>
<td>Umbelliferone</td>
<td><img src="image" alt="Umbelliferone" /></td>
<td>RN5</td>
<td>Herniarin</td>
<td><img src="image" alt="Herniarin" /></td>
</tr>
<tr>
<td>RN2</td>
<td>Scopoletin</td>
<td><img src="image" alt="Scopoletin" /></td>
<td>RN6</td>
<td>Aesculetin</td>
<td><img src="image" alt="Aesculetin" /></td>
</tr>
<tr>
<td>RN3</td>
<td>Visniadin</td>
<td><img src="image" alt="Visniadin" /></td>
<td>RN7</td>
<td>Fraxetin</td>
<td><img src="image" alt="Fraxetin" /></td>
</tr>
<tr>
<td>RN4</td>
<td>Bergapten</td>
<td><img src="image" alt="Bergapten" /></td>
<td>RN8</td>
<td>Xanthotoxin</td>
<td><img src="image" alt="Xanthotoxin" /></td>
</tr>
</tbody>
</table>

**The effectiveness of coumarins against diabetes**

Diabetes, as a significant component of metabolic syndrome, is classified into three characteristic kinds: type 1 diabetes, type 2 diabetes, and gestational diabetes\textsuperscript{36}. The primary symptoms of type 1 diabetes occur when the pancreas fails to secrete sufficient insulin as a result of metabolic process irregularities. On the other hand, type 2 diabetes has numerous consequences, such as enhanced hepatic glucose output, unusual islet-cell action, incretin system irregularities, and peripheral insulin resistance\textsuperscript{37,38}. Isofraxidin with the chemical name 7-hydroxy-6,8-dimethoxy coumarin has been found to be beneficial for treating type 2 diabetes, in mice, causing hypoglycemic and hypolipidemic alterations\textsuperscript{39}. Other coumarins, such as umbelliferone, osthole, and esculentin, have shown promising activity as applicants in diabetic treatment. The enhancement of insulin production and the restoration of pancreatic cells may assist to minimize the complications of diabetes\textsuperscript{40}.  

167
It is detected that coumarin-based compounds are efficacious in the management of infectious diseases when combined with metal ions\textsuperscript{41}. In this concern, both gastritis and diabetes can be managed more efficiently by cinnamolactone coumarins and trans-cinnamic acids when combined with zinc or magnesium salt \textsuperscript{42}. Table 3 below was recorded some coumarin products that may act as hypoglycemic applicants\textsuperscript{43}.

**Table 3: Some Coumarin derivatives that have anti-diabetic properties, and their chemical structures.**

<table>
<thead>
<tr>
<th>Code</th>
<th>Compounds name</th>
<th>Chemical structure</th>
<th>Code</th>
<th>Compounds name</th>
<th>Chemical structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>RN9</td>
<td>Ficusin</td>
<td><img src="image" alt="Ficusin" /></td>
<td>RN12</td>
<td>Alpha-lipoic acid</td>
<td><img src="image" alt="Alpha-lipoic acid" /></td>
</tr>
<tr>
<td>RN10</td>
<td>Esculin</td>
<td><img src="image" alt="Esculin" /></td>
<td>RN13</td>
<td>Scopoletin</td>
<td><img src="image" alt="Scopoletin" /></td>
</tr>
<tr>
<td>RN11</td>
<td>Scoparone</td>
<td><img src="image" alt="Scoparone" /></td>
<td>RN14</td>
<td>Decursinol</td>
<td><img src="image" alt="Decursinol" /></td>
</tr>
</tbody>
</table>

**Antihypertensive efficacy of coumarins**

In cultured cardiac cells, coumarins have been shown to have vasodilatory properties\textsuperscript{45}. Visnadine (derived from the fruit of the *Ammi visnaga* plant) has been shown to have peripheral and coronary vasodilator properties in the treatment of ischemic heart disease\textsuperscript{35}.

**The photo-toxic properties of coumarins**

The photo-activity of several coumarins, including furocoumarin, has been demonstrated, people get burned skin (phyto-photodermatitis) after being exposed to both ultraviolet radiation and furacoumarins\textsuperscript{46,47}. Psoriasis treatment with a combination of orally xanthotoxin and ultraviolet light ranging from 320 to 400 nm has been found to be beneficial\textsuperscript{48}. Besides xanthotoxin was found in products extracted from the plant *Ammi majus*, which is also utilized to cure vitiligo\textsuperscript{49}.

Because at a wavelength ranging from 300 to 360 nm coumarins do not cause phototoxic responses. So, at this wavelength, coumarins can be utilized to diagnose contact photo-dermatitis in a concentration-dependent manner\textsuperscript{50}.

*Artemia salina* is a fast and non-invasive test that may be used to detect the phototoxic potential with a huge number of samples. Phototoxicity was not found in athamantin or umbelliferone, while linear furanocoumarins were found to be
phototoxic in the following order: xanthotoxin < peucedanin < bergapten < psoralen\textsuperscript{51}.

**Effectiveness of coumarins in tuberculosis management**

The whole plant of *Fatoua pilosa* was discovered to contain various coumarins, such as xanthyletin, scopoletin, phellodenol A, bergapten, (+)-(S)-marmesin, (+)-(S)-rutaretin, psoralen, and umbelliferone. Scopoletin and umbelliferone, with minimal inhibitory concentrations of 42 and 58.3 gram per milliliter, correspondingly, were shown to be active towards *Mycobacterium tuberculosis* (H37Rv)\textsuperscript{52}. Additionally, (+)-(S)-marmesin, xanthyletin and phellodenol A showed good potency to fight this type of infection\textsuperscript{53}.

**The efficacy of coumarins against bacterial and fungal infections**

Coumarins, as secondary-metabolites, were shown moderate-to-good potency as antibacterial candidates. In particular coumarin compounds containing hydrocarbon substitutions, namely andostruthin and ammoresinol, have a high antibacterial impact on Gram-positive pathogens\textsuperscript{54}.

Novobiocin, a fungus-derived antibiotic, has been found to be effective in treating Gram-positive and G-negative bacterial infections\textsuperscript{55}. Coumaemycin also has antibacterial activity, one study revealed that coumaerycin can be greatly delayed the DNA supercoiling of *Escherichia coli*, and it is being 50\% percent more powerful than novobiocin\textsuperscript{56}.

Imperatorin, a biologically effective natural coumarin compound isolated from *Angelica archangelica* and *Angelica dahurica*, was shown to have antibacterial action against *Shigella dysenteriae*\textsuperscript{57}. Ayapin, scopolin, and scopoletin have antimicrobial effects against the head rot of sunflower. Besides, scopoline was found to have a stronger antibacterial impact versus sclerotinia than other studied compounds Table 4. Other examples about coumarins with antibacterial activity in addition to their chemical structures\textsuperscript{55,58,59}.

**Table 4: Some coumarin derivatives that have antibacterial property and their chemical structures.**

<table>
<thead>
<tr>
<th>Code</th>
<th>Compound name</th>
<th>Chemical structure</th>
<th>Code</th>
<th>Compound name</th>
<th>Chemical structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>RN15</td>
<td>Imperatorin</td>
<td><img src="image" alt="Imperatorin" /></td>
<td>RN18</td>
<td>Grandivittin</td>
<td><img src="image" alt="Grandivittin" /></td>
</tr>
<tr>
<td>RN16</td>
<td>Aegelinol</td>
<td><img src="image" alt="Aegelinol" /></td>
<td>RN19</td>
<td>Felamidin</td>
<td><img src="image" alt="Felamidin" /></td>
</tr>
<tr>
<td>RN17</td>
<td>Agasylin</td>
<td><img src="image" alt="Agasylin" /></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Coumarin compounds, reported in Table 5 antifungal activity\textsuperscript{57,58}, that coordinated with metals forming metal complexes, have also demonstrated moderate-to-good antifungal efficacy versus many pathogenic fungi, including \textit{Aspergillus flavus}, \textit{Candida albicans}, \textit{Trichophyton longijusus}, \textit{Candida glaberata}, \textit{Fusarium solani}, and \textit{Microsporum canis}\textsuperscript{60}.

**Table 5: Some coumarins compounds which have antifungal activity and their chemical structures.**

<table>
<thead>
<tr>
<th>Code</th>
<th>Compound name</th>
<th>Chemical structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>RN20</td>
<td>Scopolin</td>
<td><img src="image" alt="Scopolin structure" /></td>
</tr>
<tr>
<td>RN21</td>
<td>Ostheno3</td>
<td><img src="image" alt="Ostheno3 structure" /></td>
</tr>
<tr>
<td>RN22</td>
<td>7-O-Geranyl-esculetin</td>
<td><img src="image" alt="7-O-Geranyl-esculetin structure" /></td>
</tr>
</tbody>
</table>

According to several studies, many coumarins from natural or synthetic sources may be efficient for inhibiting acetylcholinesterase, reducing oxidative stress, and quenching the damage-related free radicals, also protecting the neurons. Accordingly, these coumarins may have the potential to act as promising applicants in curing Alzheimer's disease\textsuperscript{66,67}.

Ensacolin 1 (KA-672), a coumarin congener, has recently been demonstrated to have strong therapeutic effects, including suppression of acetylcholinesterase\textsuperscript{68}.

**The effectiveness of coumarins in fighting viral infection and their anti-HIV properties**

Several secondary-metabolites with coumarin kernel have been found to exhibit antiviral effects Figure 2. Presents several examples of coumarins with proven antiviral activity\textsuperscript{3}.
Figure 2: Various coumarins that have been utilized as antiviral and anti-HIV medicines. RN26: Inophyllum P, RN27: (+)-Calanolide A, RN28: Inophyllum C, RN29: Inophyllum E, RN30: Inophyllum A, and RN31: Inophyllum B.

Certain coumarin compounds, such as (+)-hopeyhopin, hystroxene-I, quinolinone, and hystrolinone which are found in products isolated from the roots of the *Citrus hystrix* plant are evaluated as antimicrobial and anti-HIV applicant\(^69\).

Furanocoumarin esters (fesumtuorin-A, -B, -D, -E, -F, -G, and -H) that identified in the products extracted from the dehydrated roots *Ferula sumbul* plant, have been tested for anti-HIV activity\(^70\). Also, Figure 3 displayed the chemical structures of eight bioactive hemiterpene furanocoumarin derivatives \(^71,72\).

Moreover, GUT-70 which is found in the trunk bark of *Chlorophyllum brasiliense* plant has showed a significant inhibitory action on HIV-1 cells, using necrosis-factor kappa-B as the suppressor target\(^73\).

The effectiveness of coumarin compounds as antitumor and cancer-preventive applicants

Biomedical research on coumarin compounds indicated that these compounds have a future therapeutic value for managing different types of cancer. The bulk of the research was conducted on tumors found in the brain, prostate, skin, pancreatic cells, breast, and others. One of the coumarin compounds, osthole, proved to be efficient for suppressing the metalloproteinase promoter and consequently limiting human breast cancer spread. Moreover, natural coumarin derivative named neo-tanshinlactone can effectively reduce the growth of two estrogen receptor-positive breast tumor cells, with the activity approximately ten times greater than tamoxifen.

Coumarin-monastrol hybrids were created by merging two active pharmacophores, coumarin and monastrol, as antitumor medicines, resulting in a hybrid structural strategy. The activity of these hybrids against the MDB-MB-231 and MCF-7 (breast cell adenocarcinoma) cell lines was remarkable. Apoptotic investigations, caspase-3 activation assays, and cell cycle analyses were undertaken to examine the principles behind this hybrid's anticancer efficacy. Caspase-3 activation caused death in both original and metastatic mammary tumor cells, regardless of ER (estrogen receptors) status.

Esculetin that chemically named 6,7-dihydroxy coumarin was extracted from Euphorbia lathyris, Citrus limonia, and Artemisia capillaries. This coumarin-based product can enhance cancer cell
death by up-regulating the tumor necrosis factor-related apoptosis in SAS (mouth carcinoma)\textsuperscript{78}. From the seeds of a plant known as \textit{Psoralea corylifolia}, furanocoumarins like psoralidin were isolated\textsuperscript{79,80}. These coumarins have shown a potent cytotoxic impact versus the cell populations SNU-1, SNU-16 (gastric tumor), MCF-7 (breast tumor), and HT-29 (colon tumor). Besides, psoralidin itself had been shown to cause cell death in both androgen-dependent and -independent prostates cancer cells, in addition to reducing the development of PC3 xenograft carcinomas in mice\textsuperscript{81–83}.

Coumarin-derived compounds may have anticancer action through several methods, such as deactivation of the telomerase enzyme, and inhibition of protein kinase activity, as well as suppression of oncogene transcription\textsuperscript{84}. Furthermore, researchers discovered that coumarins can restrict cancer cell growth by stopping the cell cycle in the G0/G1and/or G2/M phases, and altering cancer cell p-glycoprotein\textsuperscript{84–86}. Also, hydroxycoumarin compounds have cytotoxic action by creating free radicals in cancerous cells, resulting in oxidative stress and apoptosis\textsuperscript{86}. Additionally, coumarin derivatives were able to suppress protein kinase 2, and consequently prevent cancer cell growth\textsuperscript{87}.

**CONCLUSION**

Coumarins are natural bioactive products that have evolved as a vital component in the various interactions between plants and their inanimate environment. Coumarin compounds are beneficial to plants as endogenous protective biochemicals, and to humans as pharmaceutical supplements due to their therapeutic potential against various diseases.

**REFERENCES**


7 Bashir MK, Mustafa YF, Oglah MK. Antitumor, antioxidant, and antibacterial activities of glycosyl-conjugated compounds: A review.


13 Mustafa YF, Khalil RR, Mohammed ET. Antimicrobial activity of aqueous extracts acquired from the seeds of two apples’ cultivars. Systematic Reviews in Pharmacy 2020;11:382–387.


36 Kuzuya T, Matsuda A. Classification of Diabetes on the Basis of Etiologies Versus Degree of Insulin Deficiency.


46 Mohammed ET, Mustafa YF. Coumarins from Red Delicious apple seeds: Extraction, phytochemical analysis, and evaluation as antimicrobial agents. Systematic Reviews in Pharmacy. 2020;11(2):64-70.


48 Khalil RR, Mustafa YF. Phytochemical, antioxidant and antitumor studies of coumarins extracted from Granny Smith apple seeds by different methods. Systematic Reviews in Pharmacy. 2020;11(2):57-63.


65 Greig NH, Utsuki T, Ingram DK, et al. Selective butyrylcholinesterase


