Coumarin-based products: Their biodiversity and pharmacology

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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.

المعلومات الاساسية: تُوَلِد المملكة النباتية وتطلق مجموعة واسعة من المستقلبات الثانوية ، والتي لها تأثيرات عديدة على النظم البيولوجية والسمية والبيئية التي تعمل بطريقة مماثلة للمركبات المصنعة. واحدة من هذه المستقلبات الثانوية هي الكومارين ، والتي يتم الحصول عليها من العديد من النباتات والفطريات والبكتيريا. تشتهر الكومارين بخصائصها المضادة للسرطان والفيروسات وفيروس نقص المناعة البشرية والفطريات والبكتيريا
الغاية من الدراسة: تهدف هذه الدراسة إلى تقديم لمحة موجزة عن التنوع البيولوجي والتطبيقات الدوائية للكومارين ومشتقاته الطبيعية ، بالإضافة إلى تقييم الفوائد الطبية المستقبلية. كما فحصت بالتفصيل البيانات المتعلقة بالكومارين ومشتقاته ، لا سيما تلك المتعلقة بالأفعال الصيدلانية والبيولوجية.
الاستنتاج: آثار الكومارين على صحة الإنسان هي قضية متعددة الأوجه ، مع العديد من المخاوف بشأن السلامة والسمية من الأنظمة الغذائية والعلاجات الطبية. تركز هذه المراجعة على البحث السريري للكومارين لعلاج العديد من الأمراض المزمنة ، مثل السرطان ومرض الزهايمر وفيروس نقص المناعة البشرية والسكري ، وارتفاع ضغط الدم .
الكلمات المفتاحية: الكومارينات الطبيعية، الأنشطة الطبية الحيوية، المستقلبات الثانوية، خافض للضغط، مضاد للالتهابات.

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 [3].

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[4,5]. Although secondary-metabolites have diverse Phyto-biochemical properties, they also provide a potential ecological role in safeguarding the environment [6].

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[1,6].

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[2]. 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[7].

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[7,8]. 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[8,9]. However, the toxic effects of many coumarin and coumarin-related products remain unknown, raising concerns about their safety in medicinal treatments and dietary intake[10].

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[11]. 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[12]. 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 *Anglica archangelica* and *Pastinaca sativa* respectively[14].

Figure 1: Some significant medicinal herbs that contain various types of coumarins: 1-*Zanthoxylum schinifolium,* 2-*Pheblium clavatum,* 3-*Mallotus resinosus,* 4-*Mammea siamensis,* 5-*Artemisia keiskeana,* 6-*Ferula tingitana,* 7-*Jatropha integerrima.*

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[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[16]. Coumarins of *Dipteryx odorata*, *Cinnamomum cassica*, and *Anthoxanthum odoratumcan* can act as natural tasting and aromatic ingredients[17]. *Bilberries*, *cloudberry*, *chicory* and *green tea* are also rich in various types of coumarins[15].

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

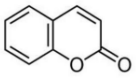
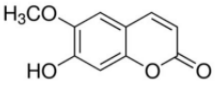
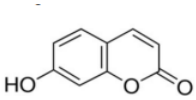
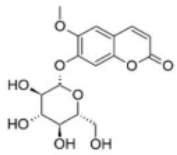
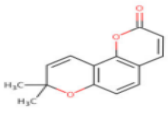
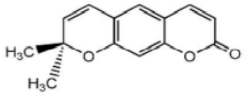
Bergapten levels are differ from the leaf to the petiole in *Apium graveolens*, furthermore , the bergapten concentrations increase throughout the seedling stage and decrease at maturity, demonstrating a seasonal pattern[19]. Also, furanocoumarin-specific bergaptol-O-methyltransferases may be only found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

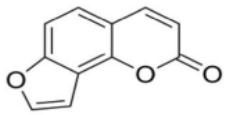
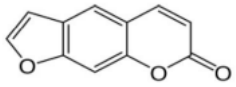
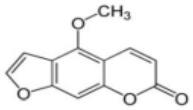
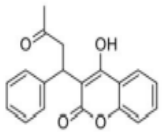
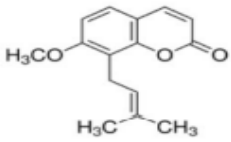
Aflatoxin B1, a natural occurring coumarin derivative, is the most often found in *Aspergillus species*. It is worth mentioning

that Aflatoxin B1 is a fungal metabolite that has the potential to be carcinogenic[21].

Coumermycin A1 and Clorobiocin have a 3-amino-4-hydroxy-coumarin moiety and may be produced from several *Streptomyces types*[22]. Besides, several coumarin-based products were isolated from celery (*Apium graveolens L. var. dulce Miller*) leaves[23], while furanocoumarins are found only in schizogenous canals of this plant seeds[24]. In cow parsnip, *Heracleum lanatum Michx*, furanocoumarins have concentrated predominantly in the petiolar and foliar canals in comparison to the laboratory or glasshouse yields[23]. 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

Categories	Characteristics	Example (s)	Structure
Simple coumarins	The benzene component of coumarin nucleus has been hydroxylated, alkoxylated, or even alkylated.	Coumarin (2*H*-chromen-2-one).	
		Scopoletin (7-hydroxy-5-methoxycoumarim).	
		Umbelliferone (7-hydroxycoumarin).	
		Scopolin (7-(β-D-Glucopyranosyloxy)-6-methoxy-2*H*-1-benzopyran-2-one).	
Pyrano-coumarins	Pyran ring is directly fused with the benzene component of coumarin nucleus.	Seselin (8,8-dimethylpyrano(2,3-f) chromen-2-one).	
		Xanthyletin (2,2-dimethylpyrano(3,2-g) chromen-8-one).	

Furano-coumarins	Furan ring is directly fused with the component of coumarin nucleus.	Angelicin (2-Oxo-(2H)-furo(2,3-h)-1-benzopyran, 2*H*-Furo(2,3-*h*)-1-benzopyran-2-one).	
		Psoralen (7*H*-Furo(3,2-*g*)(1) benzopyran-7-one).	
		Bergapten (5-Methoxypsorale).	
Pyrone-substituted coumarins	Substitution on the pyrone part of coumarin, usually at the 3-C or 4-C position.	Warfarin (RS)-4-Hydroxy-3-(3-oxo-1-phenylbutyl)- 2H-chromen-2-one).	
Benzene-substituted coumarins	Substitution on the benzene part of coumarin, usually at the 3-C or 4-C position.	Osthole 7-Methoxy-8-(3-methylbut-2-en-1-yl)-2H-1-benzopyran-2-one.	

Abiotic variables that influence coumarins content in plants

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[1,2,25]. Indeed, abiotic environmental variables that limit the synthesis of secondary-metabolites indirectly influence the plant-biotic interactions[1] .

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

Biological potentials of coumarins and their medicinal values

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

Coumarins-effectiveness against inflammation

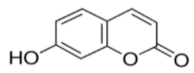
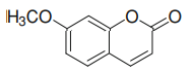
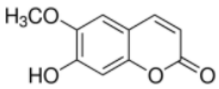
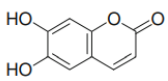
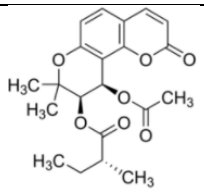
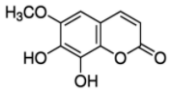
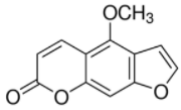
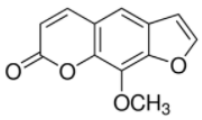
Inflammation involves creation and release of numerous mediators such as bradykinins, histamines, prostaglandins, and serotonin caused by a response to the chemical,

physical, or biological stimulation of cells[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[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[34]. Besides, umbelliprenin had been found to have *in vitro* anti-inflammatory action based on its capability to diminish the carrageenin-promoted paw edema by about 39% percent[35].

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

Code	Compounds name	Chemical structure	Code	Compounds name	Chemical structure
RN1	Umbelliferone		**RN5**	Herniarin	
RN2	Scopoletin		**RN6**	Aesculetin	
RN3	Visniadin		**RN7**	Fraxetin	
RN4	Bergapten		**RN8**	Xanthotoxin	

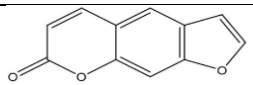
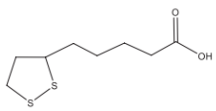
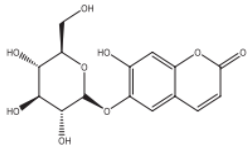
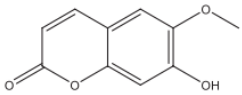
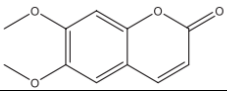
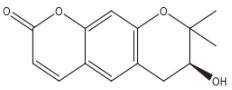
The effectiveness of coumarins against diabetes

Diabetes, as a significant component of metabolic syndrome, is classified into three characteristic kinds: type 1 diabetes, type 2 diabetes, and gestational diabetes[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[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[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[40].

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

The anti-diabetic properties of coumarin compounds isolated from *Urtica dentate* were trialed on 8-week-old mice. In comparison to the untreated group, it found a substantial decrease in insulitis, a rise in the number of pancereatic islets a 26-week delay in diabetes onset[44].

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

Code	Compounds name	Chemical structure	Code	Compounds name	Chemical structure
RN9	Ficusin		**RN12**	Alpha-lipoic acid	
RN10	Esculin		**RN13**	Scopoletin	
RN11	Scoparone		**RN14**	Decursinol	

Antihypertensive efficacy of coumarins

In cultured cardiac cells, coumarins have been shown to have vasodilatory properties[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[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 [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[48]. Besides xanthotoxin was found in products extracted from the plant *Ammi majus*, which is also utilized to cure vitiligo[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[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[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)[52]. Additionally, (+)-(S)-marmesin, xanthyletin and phellodenol A showed good potency to fight this type of infection[53].

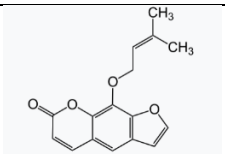
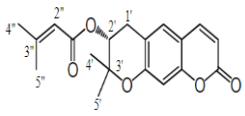
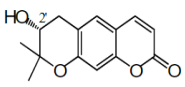
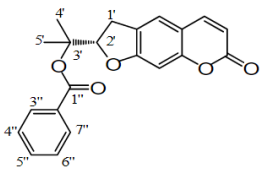
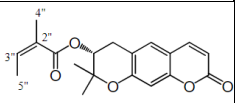
The efficacy of coumarins against bacterial and fungal infections

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[54].

Novobiocin, a fungus-derived antibiotic, has been found to be effective in treating Gram-positive and G-negative bacterial infections[55]. Coumaermycin 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[56].

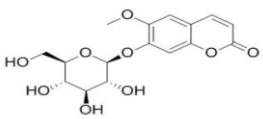
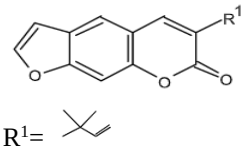
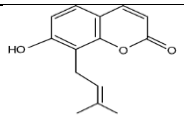
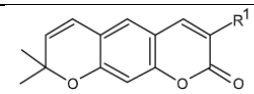
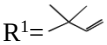
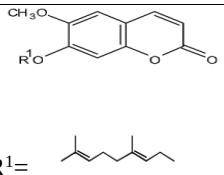
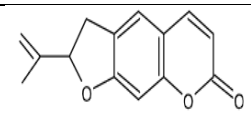
Imperatorin, a biologically effective natural coumarin compound isolated from *Angelica archangelica* and *Angelica dahurica*, was shown to have antibacterial action against *Shigella dysenteriae*[57]. Ayapin, scopolin, and scopoletin have antimicrobial effects against the head rot of sunflower. Besides, 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[55,58,59].

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

Code	Compound name	Chemical structure	Code	Compound name	Chemical structure
RN15	Imperatorin		**RN18**	Grandivittin	
RN16	Aegelinol		**RN19**	Felamidin	
RN17	Agasyllin				

Coumarin compounds, reported in Table 5 antifungal activity[57,58], that coordinated with metals forming metal complexes, have also demonstrated moderate-to-good antifungal efficacy versus many pathogenic fungi, including *Aspergillus flavus*, *Candida albicans*, *Trichophyton longifusus*, *Candida glaberata*, *Fusarium solani*, and *Microsporum* canis[60].

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

Code	Compound name	Chemical structure	Code	Compound name	Chemical structure
RN20	Scopolin		**RN23**	Dimethyl allyl psoralene	
RN21	Osthenol		**RN24**	Dimethyl allyl xanthyletin	 
RN22	7-O-Geranyl-esculetin		**RN25**	Isoangenomalin	

Coumarin compounds as a possible therapy for Alzheimer's illness

Alzheimer's disease is a neurodegenerative illness characterized by a progressive loss of cognitive, behavioural, and social abilities affecting a person's ability to function independently [61]. A combination of factors can cause Alzheimer's disease like the disruption of brain proteins which in turn results in modulating the functions of brain cells and consequently triggers a chain of harmful events[62,63]. Alzheimer's disease is also associated with a significant loss of cholinergic neurons due to deficiency of acetylcholine in certain brain areas that control learning and regular memory functioning[64]. Therefore, any substance with the ability to inhibit acetylcholinesterase and/or butyrylcholinesterase could have a potential therapeutic[65].

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[66,67].

Ensaculin 1 (KA-672), a coumarin congener, has recently been demonstrated to have strong therapeutic effects, including suppression of acetylcholinesterase[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[3].

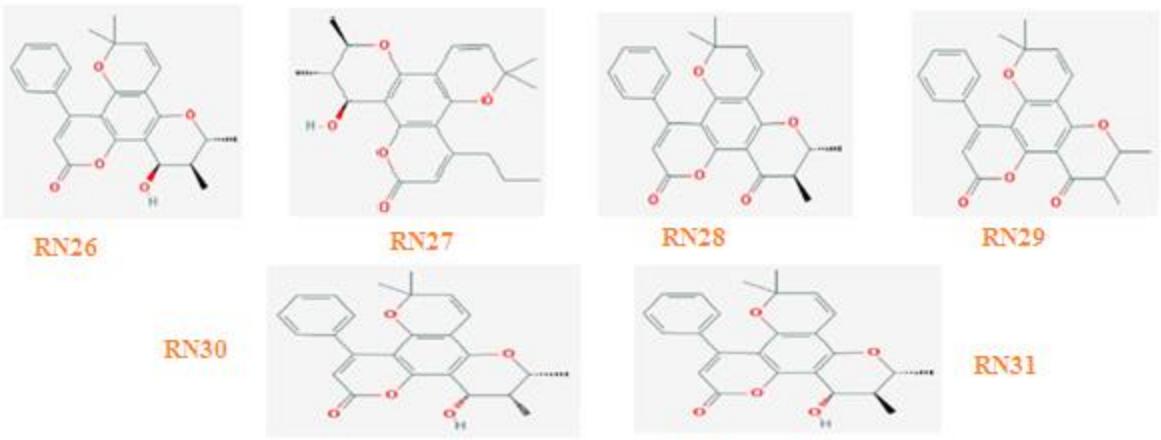


Figure 2: Various coumarins that have been utilized as antiviral and anti-HIV medicines. RN26: Inophyllum P, RN27: (+)-Calanolide A, RN28: Inophyllum C, RN29: Inophyllum E, RN30: Inophyllum A, and RN31: Inophyllum B.

Certain coumarin compounds, such as (+)-hopeyhopin, hystroxene-I, quinolinone, and hystrolinone which are found in products isolated from the roots of the *Citrus hystrixl* 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].

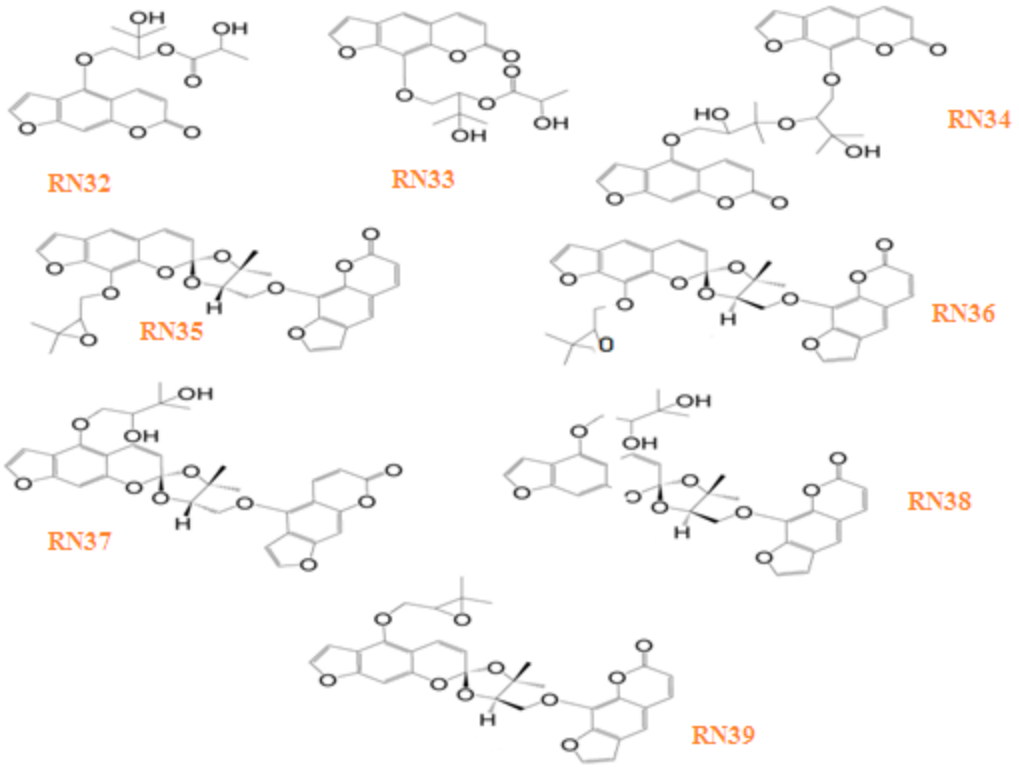


Figure 3: Eight bioactive hemiterpene coumarin derivatives. RN32: Fesumtuorin A, RN33: Fesumtuorin B, RN34: Fesumtuorin C, RN35: Fesumtuorin D, RN36: Fesumtuorin E, RN37: Fesumtuorin F, RN38: Fesumtuorin G, and RN39: Fesumtuorin H.

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

Biomedical research on coumarin compounds indicated that these compound have a future therapeutic value for managing different types of cancer[48]. 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[74]. 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[75]. 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[76]. 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[76].

Esculetin that chemically named 6,7-dihydroxy coumarin was extracted from *Euphorbia lathyris*, *Citrus limonia*, and *Artemisia capillaries*[77]. This coumarin-based product can enhance cancer cell

death by up-regulating the tumor necrosis factor-related apoptosis in SAS (mouth carcinoma)[78]. From the seeds of a plant known as *Psoralea corylifolia*, furanocoumarins like psoralidin were isolated[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[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[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[84–86]. Also, hydroxycoumarin compounds have cytotoxic action by creating free radicals in cancerous cells, resulting in oxidative stress and apoptosis[86]. Additionally, coumarin derivatives were able to suppress protein kinase 2, and consequently prevent cancer cell growth[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.

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