Natural Coumarin-Lead Compounds: A Review of Their Medicinal Potentials

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ABSTRACT

Background: Natural coumarins group, a principal member of the benzopyrone family, is one of the naturally occurring substances obtained ordinarily from plant origins, with antibacterial, anticoagulant, antihypertensive, anticancer, antioxidant, anti-inflammatory, and many other medicinal potentials. Because coumarins are found in nuts, seeds, fruits, vegetables, tea, coffee, and wine, the average person consumes a significant amount of these substances daily. Given the documented limited toxicity, relatively cheap, availability in foods, and prevalence of coumarins in numerous herbal medicines, it seems reasonable to investigate their characteristics and usage.
Objective: This review discusses naturally occurring coumarin lead substances, their extensive medicinal benefits, and official pharmacopoeia-based detection methods.
Conclusion: The medicinal potential and therapeutic uses of simple coumarins are determined by their structural substitution pattern. Because there is limited research on bioavailability for coumarins, additional research is needed to investigate the bioavailability for various coumarins, which have demonstrated good bioactivity in prior research.

Keywords: Natural coumarins, Antibacterial, Antiviral, Antihypertensive, Anticonvulsant.

المعلومات الاساسية: مجموعة الكومارين الطبيعية ، هي مركبات رئيسيه في عائلة البنزوبايرون، وهي إحدى المواد الطبيعية التي يتم الحصول عليها عادةً من أصل نباتي. تتمتع الكومارينات باستخداماتها الواسعة في العلاجات الطبية فهي تستخدم كمضادات للجراثيم، ومضادات للتخثر، ومضادات لارتفاع ضغط الدم، ومضادات للسرطان، فضلا عن استخدامات طبية أخرى عديدة. نظرًا لوجود الكومارين في المكسرات والبذور والفواكه والخضروات والشاي والقهوة والنبيذ ، فإن الشخص العادي يستهلك كمية كبيرة من هذه المواد يوميًا. بالنظر إلى قلة السمية ، والتكلفة الرخيصة نسبيًا، وتوافرها في اغذية عديدة، وانتشار الكومارين في العديد من الأدوية العشبية، يبدو من المنطقي دراسة خصائصها واستخداماتها.
الهدف من الدراسة: تناقش في هذا المقال مركبات الكومارين الطبيعية معتمدة على الصيغة الكيميائية، وفوائدها الطبية الواسعة، وطرائق الكشف عنها المعتمدة في دستور الأدوية.
الاستنتاج: يتم تحديد الفعالية الطبية والاستخدامات العلاجية للكومارينات البسيطة من خلال نمط الاستبدال التركيبي. نظرًا لوجود أبحاث محدودة حول التوافر البيولوجي للكومارين ، لذلك هنالك حاجة إلى إجراء دراسات إضافية للتوافر البيولوجي للعديد من الكومارينات، والتي أظهرت نشاطًا حيويًا جيدًا في البحوث السابقة.

الكلمات المفتاحية: الكومارينات الطبيعية، مضاد للبكتيريا، مضاد للفيروسات، خافض للضغط، مضاد للاختلاج.

INTRODUCTION

Natural coumarins, specifically those belonging to plants, seem to be driven from phenolic derivatives and typically consisted of α-pyrone and phenyl rings bonded together[1]. As secondary metabolites of bacteria, fungi, and plants, over 1300 coumarins have been recognized[2]. The Tonka bean (*Dipteryx odorataWild*) was the first source of coumarins detected and then were observed in over 150 other species in approximately 30 distinct families[3]. *Apiaceae*, *Caprifoliaceae*, *Clusiaceae*, *Guttiferae*, *Nyctaginaceae*, *Oleaceae*, *Rutaceae*, and *Umbelliferae* are some of the more prominent ones[4]. Coumarins are most abundant in the plant's fruits like Bael fruits (*Aegle marmelos*[5]) and *Tetrapleura tetraptera TAUB*[6], and seeds like Tonka beans[7], followed by the roots like *Ferulago campestris*[8], the leaves like *Murraya paniculata*[9], and the latex of the tropical rainforest tree like *Calophyllum teysmannii inophylloide*[10], green tea, as well as chicory and other foods[11].

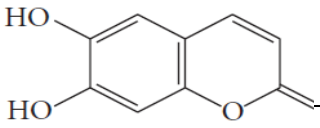
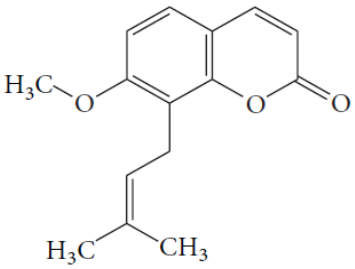
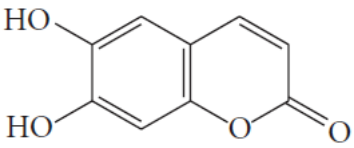
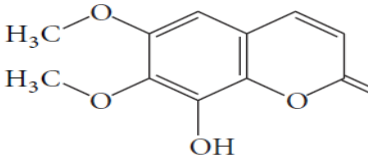
A number of essential oils, including cassia oil[12], cinnamon bark oil[13], and lavender oil[8], have significant amounts of these coumarins. Changes in the environment and seasons may have an impact on how coumarins appear in different parts of the plant[14]. Coumarins may serve as bacteriostatics, fungistatics, organizers for the growth of plants, as well as maybe wastes, but their exact role is uncertain.

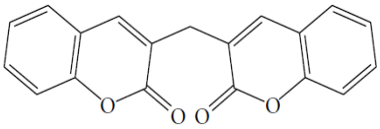
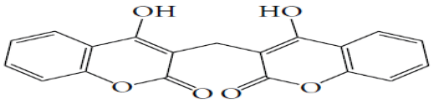
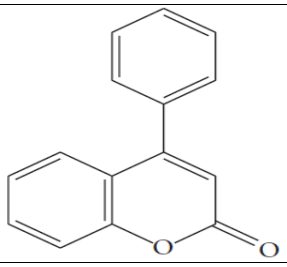
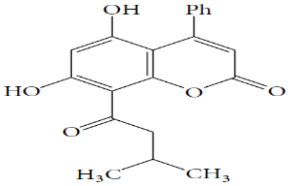
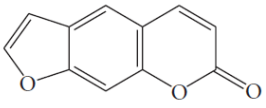
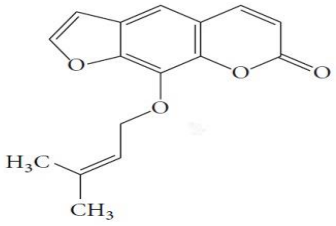
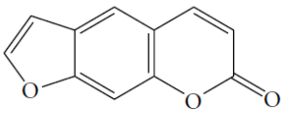
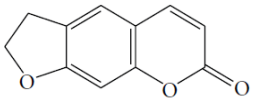
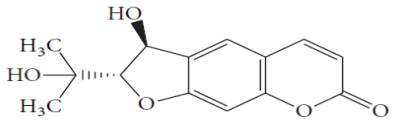
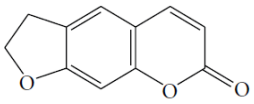
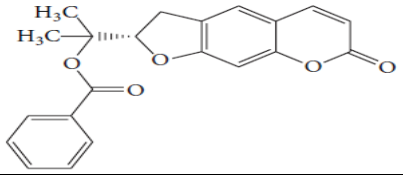
Coumarins occur naturally in a variety of forms due to the variation in the present conjugations and/or substitutions. Interestingly, the majority of biochemical and medicinal investigations on humans focused upon coumarin as well as its fundamental product of metabolism, 7-hydroxycoumarin[15].

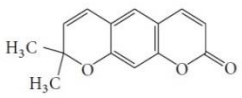
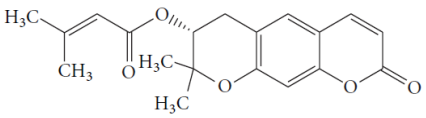
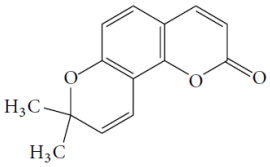
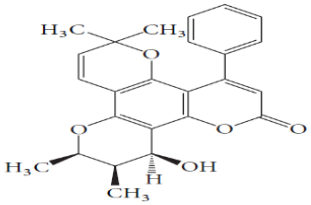
Coumarins' categorization

According to the chemical structure of the molecules, natural coumarins can be divided into six major groups, as listed in Table 1. In this Table, the names of coumarin groups and their general chemical structures were recorded. Also, examples belonging to each group with their chemical structures, natural sources, and medicinal potentials were reported.

Table 1: Various coumarin classes with some examples.

No.	Coumarin type	General structure	Examples with Structures	Sources and medicinal potentials
1	**Simple coumarins**		**Osthole** 	Osthole was obtained from *Ferulago campestris* (*Apiaceae*) roots [16]. It is used as an antioxidant, antimicrobial, antifungal, antitumor, and anticonvulsant, also in the treatment of multiple sclerosis[17].
			Esculetin 	Esculetin was obtained from *Bougainvillea spectabilis* Wild [18] and *Cichorium intybus* (*Nyctaginaceae*) [19]. It is used as neuroprotective, antioxidant, antiadipogenic, anticancer, and anti-inflammatory[20].
			Fraxidin 	Fraxidin was obtained from *Fraxinus rhynchophylla* DENCE (Oleaceae) especially, in stem bark [21]. It is used as an antiadipogenic and antihyperglycemic[22].

2	**Bicoumarins**		**Dicoumarol** 	Dicoumarol was obtained from sweet clover[23]. It is used as an anticoagulant[24].
3	**Phenyl coumarins**		**Isodispar B** 	Isodispar B was obtained from Calophyllum dispar (Clusiaceae), especially in stem bark and fruits of the plant[25].
4	**Furano coumarins**		**Imperatorin** 	Imperatorin was obtained from *Angelica archangelica* as well as *Angelica dahurica* (Umbelliferae)[26]. It is used as an antimicrobial, antifungal, antiviral anti-inflammatory, anticancer, and anticonvulsant[27].
			Psoralen 	Psoralen was obtained from the whole plants of *Fatoua pilosa*[28]. It is used as an antifungal and antituberculosis[28]. .
5	**Dihydrofurano coumarins**		**Anthogenol** 	Anthogenol was obtained from green fruits of *Aegle marmelos*[29]. It is used as an antibacterial[29].
5	**Dihydrofurano coumarins**		**Felamidin** 	Felamidin was obtained from *Ferulago campestris*(Apiaceae)[8]. It is used as an antibacterial[30].

6	**Pyranocoumarins**		**Grandivittin** 	Grandivittin was obtained from the roots of *Ferulago campestris* [8]. It is used as an antibacterial[30].
6	**Pyranocoumarins**		**Inophyllum A** 	Inophyllum A was obtained from giant African snail, *Achatina fulica*[31]. It is used as an antiviral[32].

Medicinal Potentials of Natural Coumarins

Many naturally occurring coumarins exhibit intriguing biological characteristics, according to accumulating bits of evidence over the past decades. The most important biomedical properties are displayed in Figure 1. In Table 2, the names of the reported examples with their chemical structures are inserted.

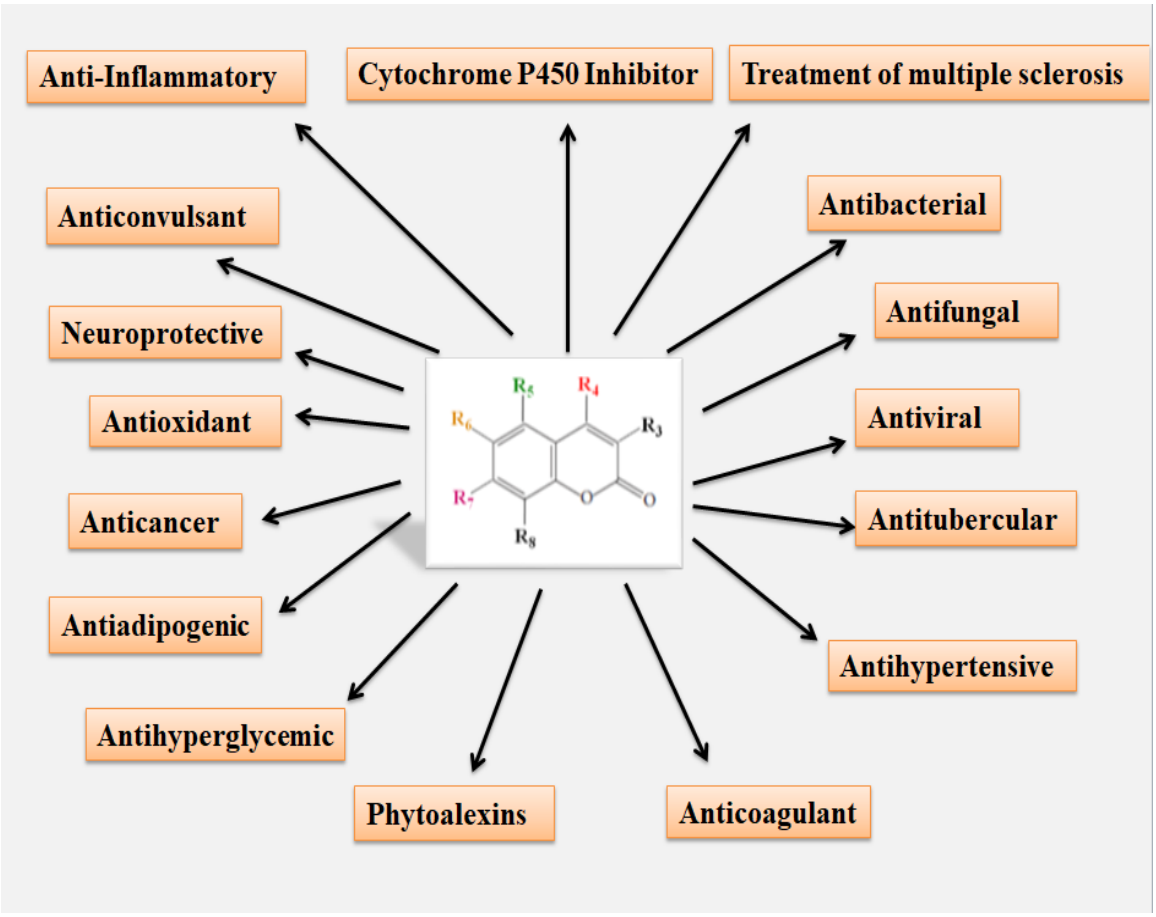


Figure 1: Schematic view of natural coumarin's-medicinal potentials.

Antibacterial Potential of Natural Coumarins

Despite the fact that coumarin (**R1**) has only modest antibacterial potential, coumarin-derived compounds with long-chain hydrocarbon substitutions demonstrated efficacy towards a variety of bacteria, including *Staphylococcus aureus*, *Bacillus megaterium*, and *Micrococcus luteus*. All the aforelisted pathogens are belonging to Gram-positive organisms.

Ammoresinol (**R2**) and ostruthin (**R3**) are two examples of these natural coumarins with the potency to act as antibacterial applicants[33]. Moreover, the coumarin-derived product termed imperatorin and symbolized here as **R4** was found to be a potential antibacterial applicant versus *Shigella dysenteriae*[34]. It is worth mentioning that **R4** was discovered and isolated from *Angelica archangelica*, as well as *Angelica dahurica* that belonging to the family commonly tagged as Umbelliferae[35]. Anthogenol (**R5**) is effective against *Enterococcus*, a dihydrofuranocoumarin extracted from the green fruits of *Aegle marmelos* [29]. From the roots of *Ferulago campestris* (Apiaceae), aegelinol benzoate (**R6**), agasyllin (**R7**), grandivittin (**R8**), and osthole (**R9**) have been isolated[16]. *Ferulago campestris* produced Felamidin (**R10**) as well[8].

Also, the significant antibacterial potential was observed in agasyllin and

aegelinol towards experimentally isolated Gram-positive and -negative types of bacteria (including *Enterobacter aerogenes*, *Enterobacter cloacae*, *Salmonella typhi*, and *Enterobacter aerogenes*). An inhibitory effect with a concentration range of 5-25mg/ml was observed against *Helicobacter pylori*, indicating antibacterial impact against this pathogen[36].

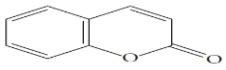
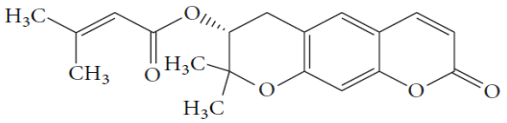
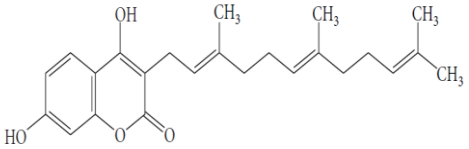
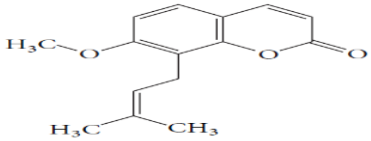
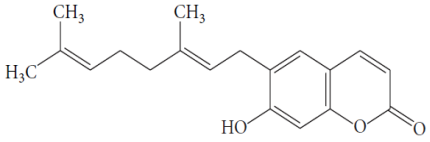
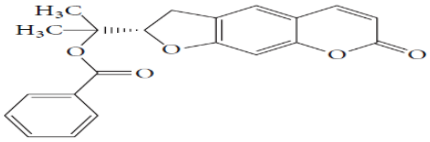
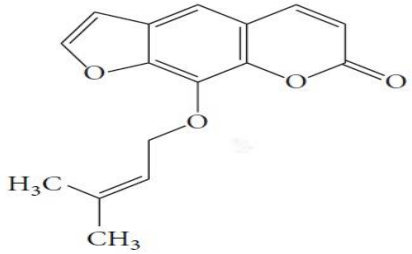
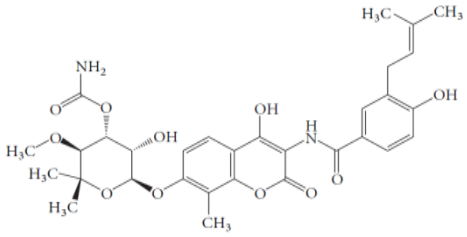
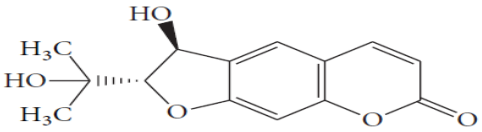
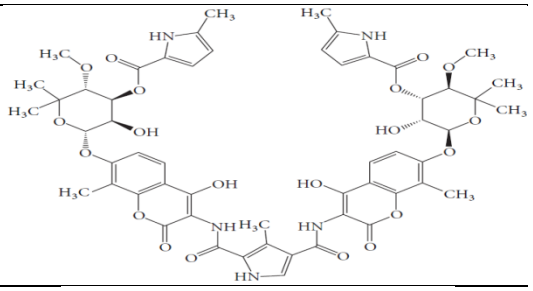
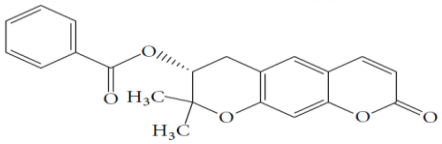
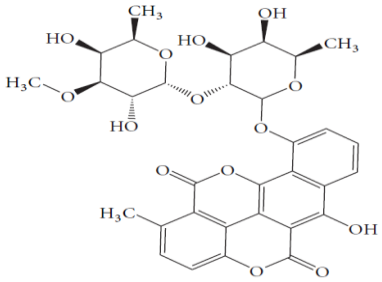
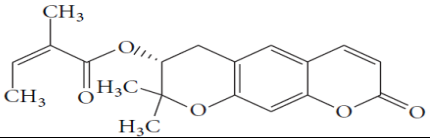
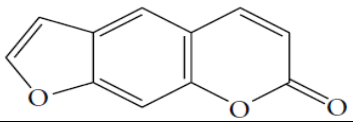
Numerous natural coumarins have been derived from the plant kingdom, but some also were identified in microorganisms. Novobiocin, coumermycin, and chartreusin are three important coumarin members extracted from microbial origins. Novobiocin (**R11**) was isolated from two mangrove-derived Streptomyces bacteria named *Streptomyces spheroids* [37] and *Streptomyces niveus*. **R11** revealed extensive antimicrobial impacts toward organisms that are Gram-positive like *Streptomyces pneumonia* pathogen, as well as Gram-negative organisms like *Haemophillus influenza* microbe [38]. Additionally, it has been proven that this natural coumarin can act as anti-pathogenic bacteria by inhibiting the bacterial DNA gyrase-phenotype [39].

Coumermycin (**R12**), a structurally related to the novobiocin antibiotic, has being approximately fifty-time most effective towards *S. aureus* and *E. coli* than novobiocin. Since **R12** can exhibit a bacteriostatic rather than bactericidal effect, the pathogenic microbes have evolved resistance over time. From the other point of view, it was found that **R12** can effectively deactivated *Escherichia coli* DNA gyrase-catalyzed DNA supercoiling[39]. Chartreusin (**R13**), a glycosidic coumarin, seems to be primarily potent towards bacteria that are Gram-positive, and was discovered in *Streptomyces chartreusis*[40]. However, the compound has not been tested for medicinal use due to its toxicity[36].

Antifungal Potential of Natural Coumarins

Osthole (**R9**) is a biologically active coumarin derivative, exhibited broad antifungal activity against phytopathogens including *Botrytis cinerea*, *Sclerotinia sclerotiorum*, and *Rhizoctonia solani*[41]. The natural sources of osthole are *Peucedanum ostruthium*[42], *Cnidium monnieri*[43], and *Angelica pubescens*[44]. A variety of coumarins have been evaluated for their antifungal potential, with the most efficient three being imperatorin (**R4**), ostruthin (**R3**), and psoralen (**R14**)[13].

Table 2: The names of the examples reported in the medicinal potentials of coumarins with their chemical structures.

Name and symbol	Chemical Structure	Name and symbol	Chemical Structure
Coumarin (R1)		**Grandivittin (R8)**	
Ammoresinol (R2)		**Osthole (R9)**	
Ostruthin (R3)		**Felamidin (R10)**	
Imperatorin (R4)		**Novobiocin (R11)**	
Anthogenol (R5)		**Coumermycin (R12)**	
Aegelinol benzoate (R6)		**Chartreusin (R13)**	
Agasyllin (R7)		**psoralen (R14)**	

Antiviral Potential of Natural Coumarins

Natural anti-HIV medicines include a wide range of compounds, including those that contain the coumarin nucleus. Novel HIV inhibitory coumarin compounds include inophyllums and calanolides. *Achatina fulica*, a giant African snail, was the source of the inophyllums-A (**R15**), -B (**R16**), -C (**R17**), -E (**R18**), -P (**R19**), -G1 (**R20**), and -G2 (**R21**)[31]. Inophyllums P and B (**R19** and **R16**), at IC_{50} readings of 130 and 38 nM, respectively, suppressed an enzyme called reverse transcriptase that is found in HIV. In cell lines, both of these coumarins have been effective towards HIV-1[32].

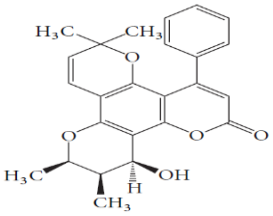
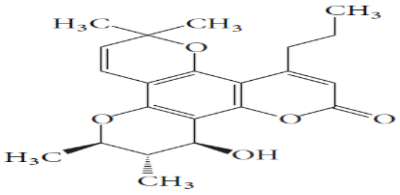
A compound called (+)-calanolide A (**R22**) was found in *Calophyllum lanigerum* leaves (*Clusiaceae*), along with an isomer called (−)-calanolide B (**R23**). Calanolides A and B were 100 percent effective against HIV-1 replication [45]. **R22** is a non-nucleoside reverse transcriptase inhibitor with high anti-HIV-1 potency. There are antiviral characteristics in **R22** that is equivalent to those of **R23** and (−)-dihydrocalanolide B (**R24**) [46 47].

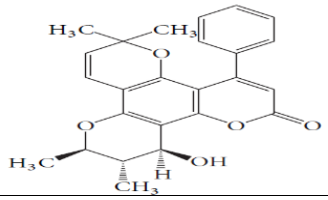
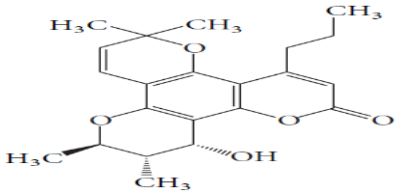
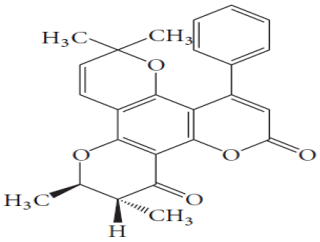
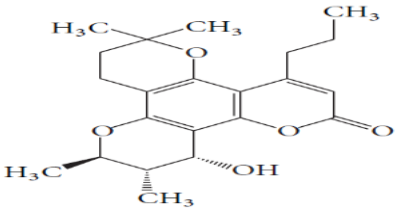
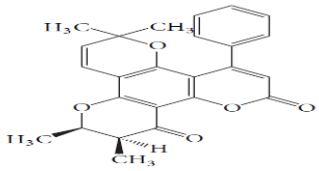
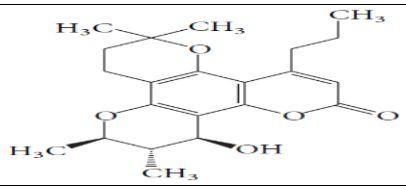
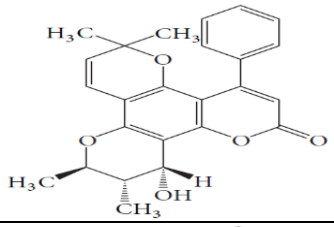
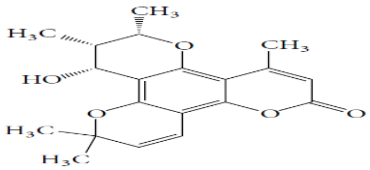
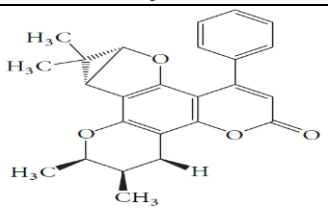
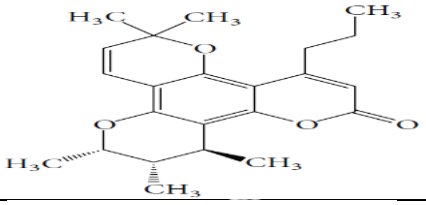
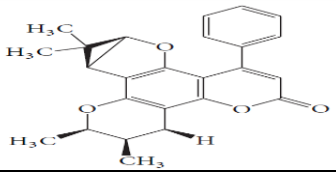
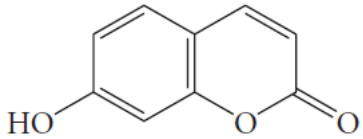
(+)-Dihydrocalanolide A (**R25**) and **R22** are being stable at a pH of 7.0 and investigated for HIV cures. Though, after 1 hour at pH < 2.0, 73 percent of **R22** had been transformed into **R23**, whereas 83 percent of **R25** had been transformed into **R24** [46 47].

R23 and **R15** were formerly obtained from the oils of *Calophyllum cerasiferum* Vesque and *Calophyllum inophyllum Linn* seeds, respectively. They are indeed members of the plant family, named *Clusiaceae*. They have been shown to be impactful HIV-1 reverse transcriptase inhibitors[7].

The anti-HIV potential was also found in pseudocordatolide C (**R26**) and calanolide F (**R27**), pyranocoumarins that were obtained from *Calophyllum lanigerum* var. austrocoriaceum and *Calophyllum teysmannii* var. inophylloide (King) P. F. Stevens (*Clusiaceae*)[48]. Finally, in various HeLa cells as well as T-cell lines, gp160-enveloped recombinant HIV-1 infection or vesicular stomatitis virus pseudotyped blocks by imperatorin (R4) [49].

Table 2: Continued

Name and symbol	Chemical Structure	Name and symbol	Chemical Structure
Inophyllum A (R15)		**(+)-calanolide A (R22)**	

Inophyllum B (R16)		**(−)-calanolide B (R23)**	
Inophyllum C (R17)		**Dihydrocal-anolide B (R24)**	
Inophyllum E (R18)		**(+)-dihydroc-alanolide A (R25)**	
Inophyllum P (R19)		**Pseudocordat-olide C (R26)**	
Inophyllum G1 (R20)		**calanolide F (R27)**	
Inophyllum G2 (R21)		**Umbelliferone (R28)**	

Antitubercular Potential of Natural Coumarins

Umbelliferone (**R28**) is a functionalized coumarin present in numerous plants and observed by distilling resins from the *Umbellifera* family[21].

From the entire plants of *Fatoua pilosa*, phellodenol A (**R29**), psoralen (**R14**), umbelliferone (**R28**) and bergapten (**R30**), (+)-(S)-marmesin (**R31**), xanthyletin (**R32**), (+)-(S)-rutaretin (**R33**), and scopoletin (**R34**) were extracted and isolated. Umbelliferone and scopoletin have MIC readings of between 58.3 and 42 μg/ml, respectively, against *Mycobacterium tuberculosis* H37Rv[28].

Xanthyletin, phellodenol A, and (+)-(S)-marmesin are active at 60 g/ml, while the other corresponding compounds are effective at more than 119 g/ml.

Phellodenol A is subsequently identified and extracted from Phellodendron amurense var. wilsonii leaves[50].

Anticoagulant Potential of Natural Coumarins

It was discovered that sweet clover contains dicoumarol (**R35**)[23], a coumarin-based compound with anticoagulant properties[24]. Coumarins seem to be vitamin K blockers that act as anticoagulants via inhibiting the cyclic inter-conversion of both vitamin K and vitamin K epoxide[51]. As depicted in Figure 2, upon N-termini of VKD proteins, vitamin K could be a cofactor for the posttranslational carboxylation of glutamate residues to the corresponding γ- carboxyglutamates [52].

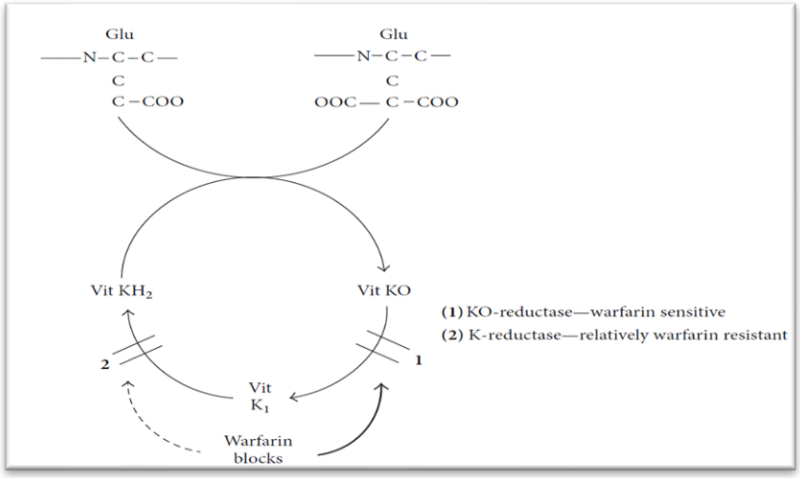


Figure 2: The vitamin K cycle and impact of warfarin, a coumarin analog.

The biological effectiveness of the clotting factors-II, -VII, -IX, and -X is γ -carboxylation dependent. Coumarins have anticoagulant impacts because they block the conversional cycle of vitamin K, causing the liver to create partly carboxylated and decarboxylated proteins of lower pro-coagulant potential[53]. vitamin K antagonists also have the potential to be pro-coagulants, because carboxylation of the anticoagulant regulatory proteins S as well as C blocked by them. Carboxylation changes the conformation of coagulation proteins in the presence of calcium ions, enhancing binding to cofactors on phospholipid surfaces[54].

Administration of vitamin K antagonists exhausts vitamin KH_2, leading to the inhibition of γ-carboxylation of VKD coagulation proteins. Since the last stage of reductase framework is comparatively unsusceptible towards the antagonists of the K vitamin, vitamin K1 (ingested or supplied clinically) can prevent the impact of coumarins. In hepatocellular regions, the K1 vitamin concentrates and seems to be ready for reductase that is unsusceptible to coumarin[55].

Anti-metabolic syndrome Potential of Natural Coumarins

A novel coumarin called dihydromammea C/OB (**R36**) was extracted first from seeds of the *Mammea africana Sabine* (*Guttiferae*) tree in West Africa[56]. Stem barks' extracts of *Mammea africana*, prepared

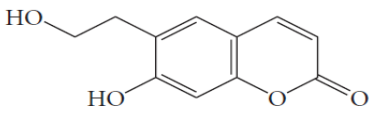
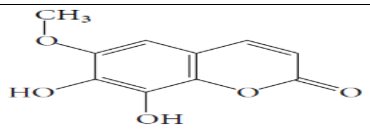
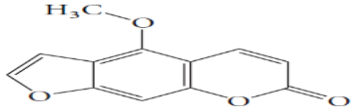
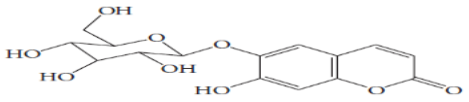
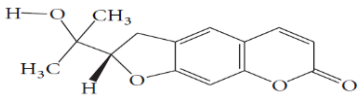
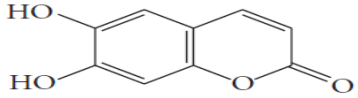
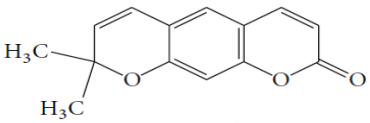
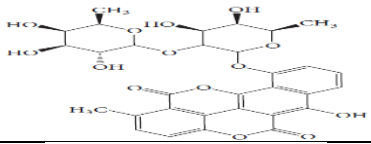
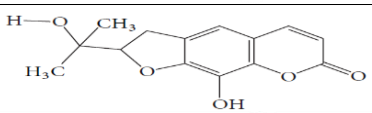
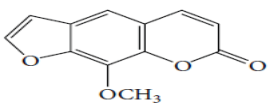
by employing dichloromethane and methanol as extracting solvents, have exhibited antihypertensive effects with Nω-nitro-L-arginine methylester-produced hypertension in males albino rats. The rats used in this trial weighed between 300 and 250 grams and were 16 to 12 weeks old[57]. Also, both of the previous mentioned extracts have displayed enhanced positive modifications in the metabolism as well as considerable anti-hyperglycemic impact through streptozotocin-stimulated diabetic males albino rats[58]. Coumarin itself has also been shown to have vasodilatory impact in cultivated myocytes[59].

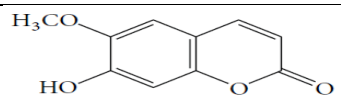
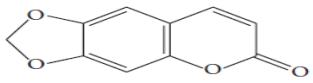
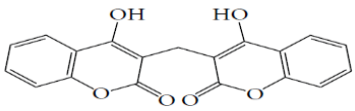
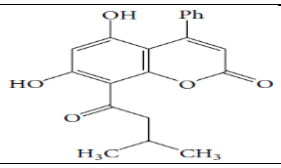
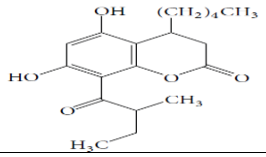
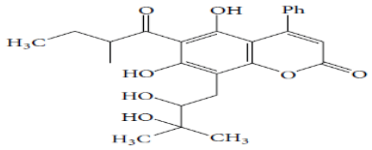
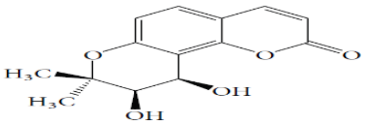
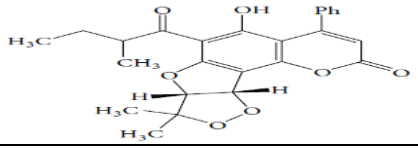
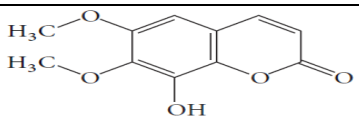
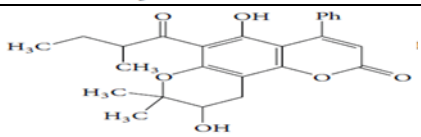
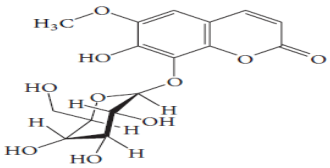
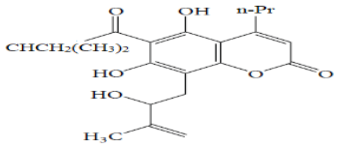
An active component named visnadine and derived from *Ammi visnaga*, especially from its corresponding fruit, has been traditionally used to treat angina pectoris. This coumarin product possesses peripheral and coronary vasodilator properties [60].

R34 is a smooth muscle relaxant that was extracted from *Tetrapleura Tetraptera* Taub of the family named *Mimosaceae*, especially from its corresponding fruit. **R34** causes hypotension among lab mice both *in vivo* & *in vitro* [6]. Additionally, Khellactone (**R37**) was also found to have vasodilatory properties, and was discovered in *Phlojodicarpus sibiricus*[61].

Fraxidin (**R38**) exhibited antihyperglycemic potential, reduced the production of inducible nitric oxide synthase[62]. In the other side and especially in stem barks of the plant named *Fraxinus rhynchophylla* (Dence) of the *Oleaceae* family, fraxidin (**R38**), fraxin (**R39**), fraxetin (**R40**), esculin (**R41**), esculetin (**R42**), and **R34** have been extracted. By using an *in vitro* assay technique, **R42** demonstrated the most powerful anti-adipogenic action against the preadipocyte cell line termed 3T3-L1 [21].

Table 2: Continued

Name and symbol	Chemical Structure	Name and symbol	Chemical Structure
Phellodenol A (R29)		**Fraxetin (R40)**	
Bergapten (R30)		**Esculin (R41)**	
(+)-(S)-Marmesin (R31)		**Esculetin (R42)**	
Xanthyletin (R32)		**3"Demethyl-cartreusin (R43)**	
(+)-(S)-Rutaretin (R33)		**Methoxsalen (R44)**	

Scopoletin (R34)		**Ayapin (R45)**	
Dicoumarol (R35)		**Isodispar B (R46)**	
Dihydromam mea C/OB (R36)		**Dispardiol B (R47)**	
Khellactone (R37)		**Mammea A/AB dioxalano-cyclo F(R48)**	
Fraxidin (R38)		**Mammea A/AB cyclo E (R49)**	
Fraxin (R39)		**Disparpropy-linol B (R50)**	

Anticancer Potential of Natural Coumarins

R42 has the anticancer potential [63] and can prevent N-methyl-D-aspartate toxicity in cultured primary neurons [64]. Also, **R4** was also found to have antitumor activity [65], while **R1** discovered to have cytotoxic effects when extracted from cassia leaf oil [12]. From another point of view, **R39** was found to protect human umbilical vein endothelial cells from hydrogen peroxide-induced cytotoxicity [66].

R9, through wound healing and trans-well experiments, showed that it could suppress the breast malignant cells' spreading and invading. This coumarin can suppress matrix metalloproteinase-s promoter and luciferase, which could be one of the reasons for **R9**'s prevention of migration and invasion [67].

R13 has been demonstrated to be an anticancer in murine L1210 and B16 melanoma, as well as P388 leukemias [68]. 3''-Demethylchartreusin (**R43**) is an unprecedented anti-neoplastic antibiotic generated by *Streptomyces chartreusis*, comprising similar aglycone but different sugar groups. It's a chartreusin structural equivalent[68] .

Finally, **R6**, **R7**, **R8**, and **R9** were slightly cytotoxic toward the A549 lung cancer cell line. All four were extracted from the plant named *Ferulago campestris* [8].

Antioxidant Potential of Natural Coumarins

R42 was found to be a promising antioxidant in many research reports [69]. Also, **R40**, at elevated concentrations (0.5mM), demonstrated free radical-scavenging potential, as well as cell protection against hydrogen peroxide mediated oxidative stress [66]. Besides, **R42** and **R39** that found in the fruits and stems of *Actinidia chinensis* and *Actinidia deliciosa* (kiwifruit) have revealed a noted activity as antiradicals versus several damaging free radicals [70]. Moreover, **R6**, **R7**, **R9**, and **R8**, had all been assessed for their antioxidant potential, using whole blood leukocytes and isolated polymorphonucleated chemiluminescence in humans [16].

Anti-Inflammatory Potentials of Natural Coumarins

It is found that **R1** has anti-inflammatory features and can be utilized to treat edema by promoting phagocytosis, enzyme synthesis, and consequently proteolysis, which eliminate protein and edema fluid from wounded tissue [71].

R4, another coumarin-based product, has anti-inflammatory potential in a carrageenan-invigorated murine-paw edema fashion *in vivo* and lipopolysaccharide-induced murine macrophages *in vitro*. Through these assays, **R4** can inhibit the production of a protein of both cyclooxygenase-2 as well as nitric oxide synthase of inducible type[72].

R42 has demonstrated anti-inflammatory potential in rat colitis caused by trinitrobenzene-sulfonic acid [73] [74]. This coumarin-based product was derived from *Bougainvillea spectabilis* Wild [4] and *Cichorium intybus* [18]. It can block the enzymes of the inflammatory response including cyclooxygenases and lipoxygenases, as well as superoxide anion production in neutrophils [75].

Anticonvulsant Potential of Natural Coumarins

It is reported that **R4** may exhibit an anticonvulsant activity in mice, with ED_{50} values ranging from 290 to 167 milligram per kilogram. The **R4**'s TD_{50} readings spanning from 329 to 443 mg/kg, according to severe neurotoxicity impacts of chimney experiment [35]. Also, **R9** may exhibit an anticonvulsant activity in mice, with ED_{50} values ranging from 253 to 639 mg/kg and acute neurotoxicity spanning from 531 to 648 mg/kg[76].

Neuroprotective Potential of Natural Coumarins

R42, when given intra-cerebroventricularly 30 minutes at a concentration of 20 μg/ml prior to ischemia, can exhibit neuroprotective benefits in a middle-cerebral artery blockage in mice fashion [77].

Cytochrome P-450 Inhibiting Potential of Natural Coumarins

Methoxsalen (**R44**) was identified in *Umbelliferae* family products, specifically in the seeds of the plant *Ammi majus*, also demonstrated *in vitro* potency as a microsomal P-450 inhibitor [78], as well as impacted on human cytochrome P-450 2A6 efficiency with a single dosage[79].

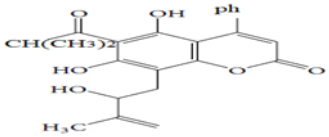
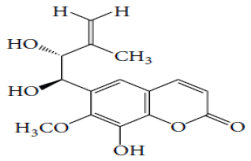
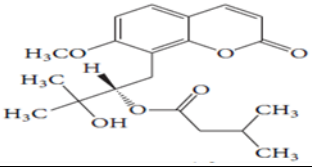
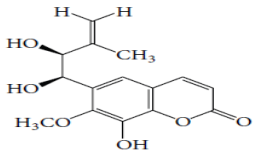
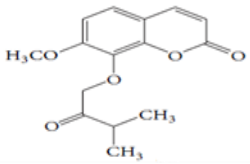
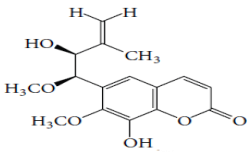
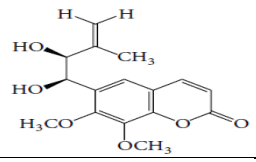
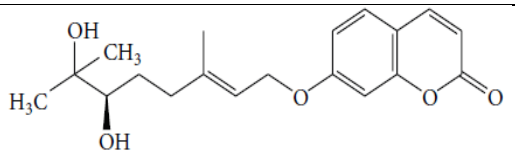
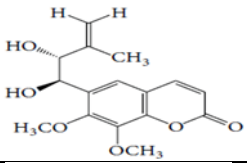
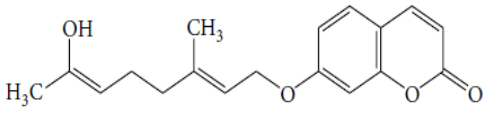
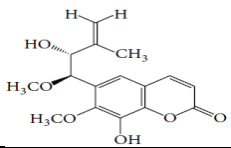
Multiple sclerosis treatment with Natural Coumarins

It is proposed and reported that the coumarin-based product symbolized as **R9** can represent as a medicinal therapy in patients with multiple sclerosis[80].

Natural Coumarins functionalized as phytoalexins

Plants create phytoalexins, some of them are derived from coumarin chemical nucleus, in response to pathological processes like fungal infection, chemical injury, as well as physical harm. Invading elements, including viruses, insects, and bacteria, are typically suppressed or killed by phytoallexins[81]. Ayapin (**R45**), a 6,7-methylenedioxycoumarin, was first discovered from *Eupatorium ayapana* (*Asteraceae*)[82]. This coumarin-based product was later extracted from a variety of additional plants, including *Artemisia apiacea*[36], *Helianthus annuus*[83], *Pterocaulon polystachyum*[84], and *Pterocaulon virgatum*[85].

Table 2: Continued

Name and symbol	Chemical Structure	Name and symbol	Chemical Structure
Disparinol D (51)		**(+)-Fatouain C (R57)**	
Murrayatin (R52)		**(−)-Fatouain D (R58) (+)-Fatouain G (R58)**	
7-Methoxy-8-(3-methyl-2-oxobutoxy)-2H-chromen-2-one (R53)		**(−)-Fatouain F (R59)**	
(+)-Fatouain A (R54)		**Marmin (R60)**	
Prenylcoumarins (+)-fatouain A (R55)		**Aurapten (R61)**	
(+)-Fatouain E (R56) (+)-Fatouain H (R56)			

Coumarin Detection from Numerous Sources and Their Structural Description

Coumarin-based products can present in different parts of various plants, and Table 3 gives a simple idea about that.

Table 3: Types of coumarins and their natural sources.

Name and symbol of coumarin-based product	Source (s)
Isodispar B (**R46**) Dispardiol B (**R47**) Mammea A/AB dioxalanocyclo F (**R48**) Mammea A/AB cyclo E (**R49**) Disparpropylinol B (**R50**) Disparinol D (**R51**)	*Calophyllum dispar* of the family *Clusiaceae*, especially stem bark and fruits of the plants[86].
Coumarin (**R1**)	Essential and seed oils like lavender and cinnamon bark oils from the roots of the plant named *Ferulago campestris* [8].
Murrayatin (**R52**)	The leaves of both *Murraya paniculata* and *Murraya exotica*[87].
7-Methoxy-8-(3-methyl-2- oxobutoxy)-2H-chromen-2-one (**R53)**	The leaves of Murraya paniculata[87].
(+)-Fatouain A (**R54**) Prenylcoumarins (+)-fatouain A (**R55**) (+)-Fatouain E (**R56**) (+)-Fatouain C (**R57**) (−)-Fatouain D (**R58**) (−)-Fatouain F (**R59**) (+)-Fatouain G (**R58**) (−)-Fatouain H (**R56**)	*Fatoua pilosa's* entire plant [88].
Marmin (**R60**)	*Aegle marmelos* (L.) Correa bark, ordinarily named Bael (*Rutaceae*)[89].
Imperatorin (**R4**) Aurapten (**R61**)	*Aegle marmelos* (L.) Correa fruit, ordinarily named Bael (*Rutaceae*)[89].

Coumarins-Analysis Using Various Techniques

Chromatography-dependent techniques involving high-performance liquid chromatography(HPLC), gas chromatography(GC), thin-layer chromatography (TLC), and paper chromatography (PC), spectrophotometry-dependent methods

including polarographic and colorimetric, and titrimetric methods are all used to isolate and analyze natural coumarins [90].

CONCLUSION

This review discusses naturally occurring coumarin lead substances, their extensive medicinal benefits, and official pharmacopoeia-based detection methods. Naturally occurring coumarins are attractive to medicinal chemists because of their biological and pharmacological characteristics, which brings them in for further screening as a variety of potential therapeutic medicines. The medicinal potential and therapeutic uses of simple coumarins are determined by their structural substitution pattern. Because there is limited research on bioavailability for coumarins, additional research is needed to investigate the bioavailability for various coumarins, which have demonstrated good bioactivity in prior research.

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