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Review Article

Review on Natural Coumarin Lead Compounds for Their Pharmacological Activity

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Coumarin (2*H*-1-benzopyran-2-one) is a plant-derived natural product known for its pharmacological properties such as anti-inflammatory, anticoagulant, antibacterial, antifungal, antiviral, anticancer, antihypertensive, antitubercular, anticonvulsant, antiadipogenic, antihyperglycemic, antioxidant, and neuroprotective properties. Dietary exposure to benzopyrones is significant as these compounds are found in vegetables, fruits, seeds, nuts, coffee, tea, and wine. In view of the established low toxicity, relative cheapness, presence in the diet, and occurrence in various herbal remedies of coumarins, it appears prudent to evaluate their properties and applications further.

1. Introduction

Coumarins (2*H*-1-benzopyran-2-one) (**1**) consist of a large class of phenolic substances found in plants and are made of fused benzene and α-pyrone rings [1]. More than 1300 coumarins have been identified as secondary metabolites from plants, bacteria, and fungi [2]. The prototypical compound is known as 1,2-benzopyrone or, less commonly, as *o*-hydroxycinnamic acid and lactone, and it has been well studied. Coumarins were initially found in tonka bean (*Dipteryx odorata* Wild) and are reported in about 150 different species distributed over nearly 30 different families, of which a few important ones are Rutaceae, Umbelliferae, Clusiaceae, Guttiferae, Caprifoliaceae, Oleaceae, Nyctaginaceae, and Apiaceae. (See Scheme 1.)

Although distributed throughout all parts of the plant, the coumarins occur at the highest levels in the fruits (Bael fruits (*Aegle marmelos*) [3], *Tetrapleura tetraptera* TAUB (Mimosaceae) [4], bilberry, and cloudberry), seeds (tonka beans) (*Calophyllum cerasiferum* Vesque and *Calophyllum inophyllum* Linn) [5] followed by the roots (*Ferulago campestris*) [6], leaves (*Murraya paniculata*) [7], *Phellodendron amurense* var. *wilsonii* [8], and latex of the tropical rainforest tree *Calophyllum teysmannii* var. inophylloide [9] green tea and other foods such as chicory. They are also found at high levels in some essential oils such as cassia oil [10], cinnamon bark oil [11], and lavender oil [6]. Environmental conditions and seasonal changes could influence the incidence of coumarins in varied parts of the plant. The function of coumarins is far from clear, although suggestions include plant growth regulators, bacteriostats, fungistats, and even waste products [12].

Biosynthesis of coumarin is reviewed by Bourgaud et al. [11]. There are types of coumarins found in nature due to various permutations brought about by substitutions and conjugations; however, most of the pharmacological and biochemical studies have been done on coumarin itself and on its primary metabolite, 7-hydroxycoumarin in man [13]. Some of this earlier pharmacological work on coumarin has been reviewed [14], and other more comprehensive reviews [13, 15, 16] deal with the occurrence, chemistry, and biochemical properties of both simple and more complex natural coumarins.

2. Classification of Coumarins

Natural coumarins are mainly classified into six types based on the chemical structure of the compounds (Table 1).

Table 1: Different coumarin types and their pharmacological properties.

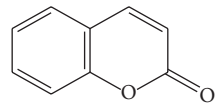
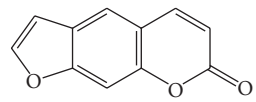
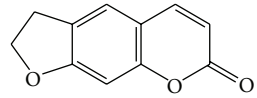
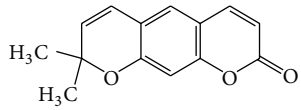
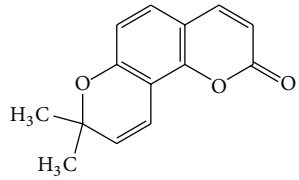
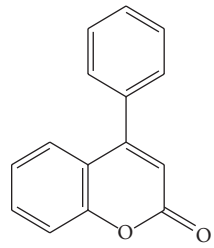
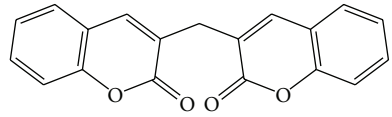
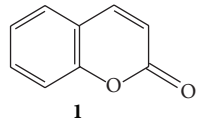
Sl no.	Type of coumarin	General chemical structure	Example with reference	Pharmacological activity
1	Simple coumarins		Coumarin [17]	Anti-inflammatory
			Esculetin [18]	Anti-inflammatory Anticancer Antiadipogenic Antioxidant Neuroprotective
			Ammoresinol [19]	Antibacterial
			Ostruthin [19]	Antibacterial Antifungal
			Osthole [20]	Antibacterial Antifungal Anticancer Anticonvulsant Antioxidant
			Novobiocin [21]	Antibacterial
			Coumermycin [22]	Antibacterial
			Chartreusin [23]	Antibacterial Antitumor
			Fraxin [24]	Anticancer Antiadipogenic Antioxidant
			Umbelliferone [25]	Antitubercular
			Fraxidin [26]	Antiadipogenic Antihyperglycemic
			Phellodenol A [8]	Antitubercular
			Esculin, fraxetin [27]	Antiadipogenic,
			Murrayatin [28] Auraptene [29]	
2	Furano coumarins		Imperatorin [17]	Anti-inflammatory Antibacterial Antifungal Antiviral Anticancer Anticonvulsant
			Psoralen [11]	Antifungal Anti-TB
			Bergapten [25]	Anti-TB
			Methoxsalen [30]	Cytochrome P450 inhibitor
			Marmalde, marmelosin [29]	
3	Dihydrofurano coumarins		Anthogenol [31]	Antibacterial
			Felamidin [6]	Antibacterial
			Marmesin, rutaretin [25]	Anti-TB Anti-TB
4	Pyrano coumarins are of two types			
4a	Linear type		Grandivittin [32]	Antibacterial
			Agasyllin [32]	Antibacterial
			Aegelinol benzoate [32]	Antibacterial
			Xanthyletin [25]	Anti-TB

Table 1: Continued.

Sl no.	Type of coumarin	General chemical structure	Example with reference	Pharmacological activity
4b	Angular type		Inophyllum A, B, C, E, P, G_1, and G_2 [33] Calanolide A, B, and F [34] (+)-Dihydrocalanolide A and B [35] Pseudocordatolide C [36]	Antiviral Antiviral Antiviral Antiviral
5	Phenyl coumarins		Isodispar B, dispardiol B, mammea A/AB cyclo E, mammea A/AB dioxalanocyclo F, disparinol D, disparpropylinol B [37]	
6	Bicoumarins		Dicoumarol [38]	Anticoagulant



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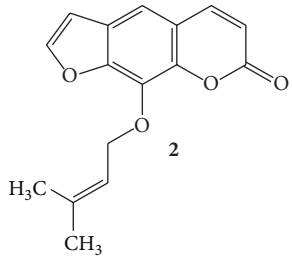
Scheme 1



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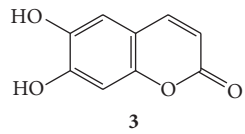

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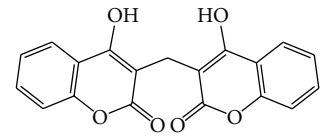
Scheme 2

The physicochemical properties and therapeutic applications of natural coumarins depend upon the pattern of substitution.

3. Coumarins and Pharmacological Activity

3.1. Coumarins for Anti-Inflammatory Activity. Coumarin (**1**) exhibits anti-inflammatory property and is used in the treatment of oedema. This removes protein and oedema fluid from injured tissue by stimulating phagocytosis, enzyme production, and thus proteolysis [17]. Another compound imperatorin (**2**) also shows anti-inflammatory activity in lipopolysaccharide-stimulated mouse macrophage (RAW264.7) *in vitro* and a carrageenan-induced mouse paw edema model *in vivo*. Imperatorin blocks the protein expression of inducible nitric oxide synthase and cyclooxygenase-2 in lipopolysaccharide-stimulated RAW264.7 [39]. Esculetin (**3**) was isolated from *Cichorium intybus* [40] and *Bougainvillea spectabilis* Wild (Nyctaginaceae) [41]. It exhibited anti-inflammatory activity in rat colitis induced by trinitrobenzenesulfonic acid [18, 42]. Esculetin (**3**) inhibits the cyclooxygenase and lipoxygenase enzymes, also of the neutrophil-dependent superoxide anion generation [43]. (See Scheme 2.)



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Scheme 3

3.2. Coumarins for Anticoagulant Activity. Dicoumarol (**4**) was found in sweet clover [1] and exhibited anticoagulant activity [38]. (See Scheme 3.)

Coumarins are vitamin K antagonists that produce their anticoagulant effect by interfering with the cyclic interconversion of vitamin K and its 2,3 epoxide (vitamin K epoxide) [44]. Vitamin K is a cofactor for the posttranslational carboxylation of glutamate residues to γ-carboxyglutamates on the *N*-terminal regions of vitamin K-dependent proteins (Figure 1) [45–50].

These coagulation factors (factors II, VII, IX, and X) require γ-carboxylation for their biological activity. Coumarins produce their anticoagulant effect by inhibiting

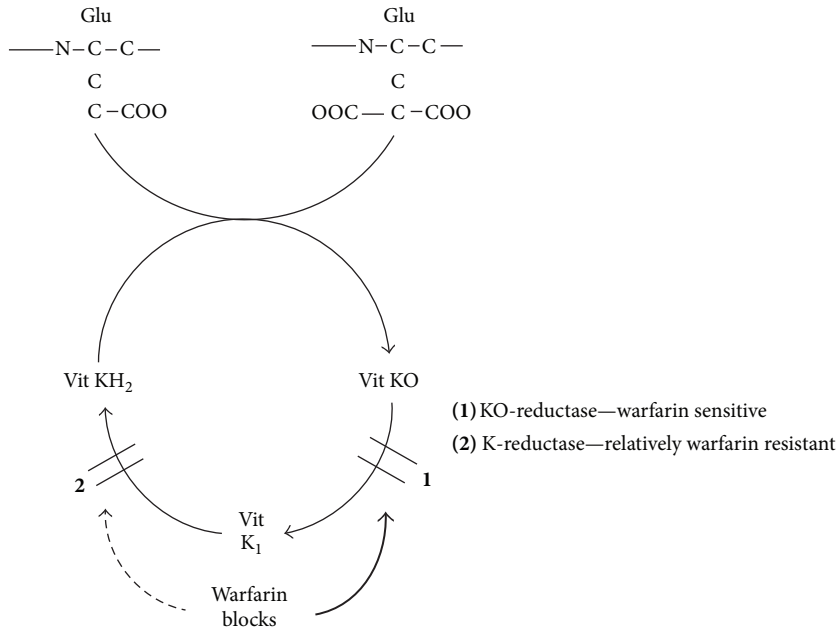
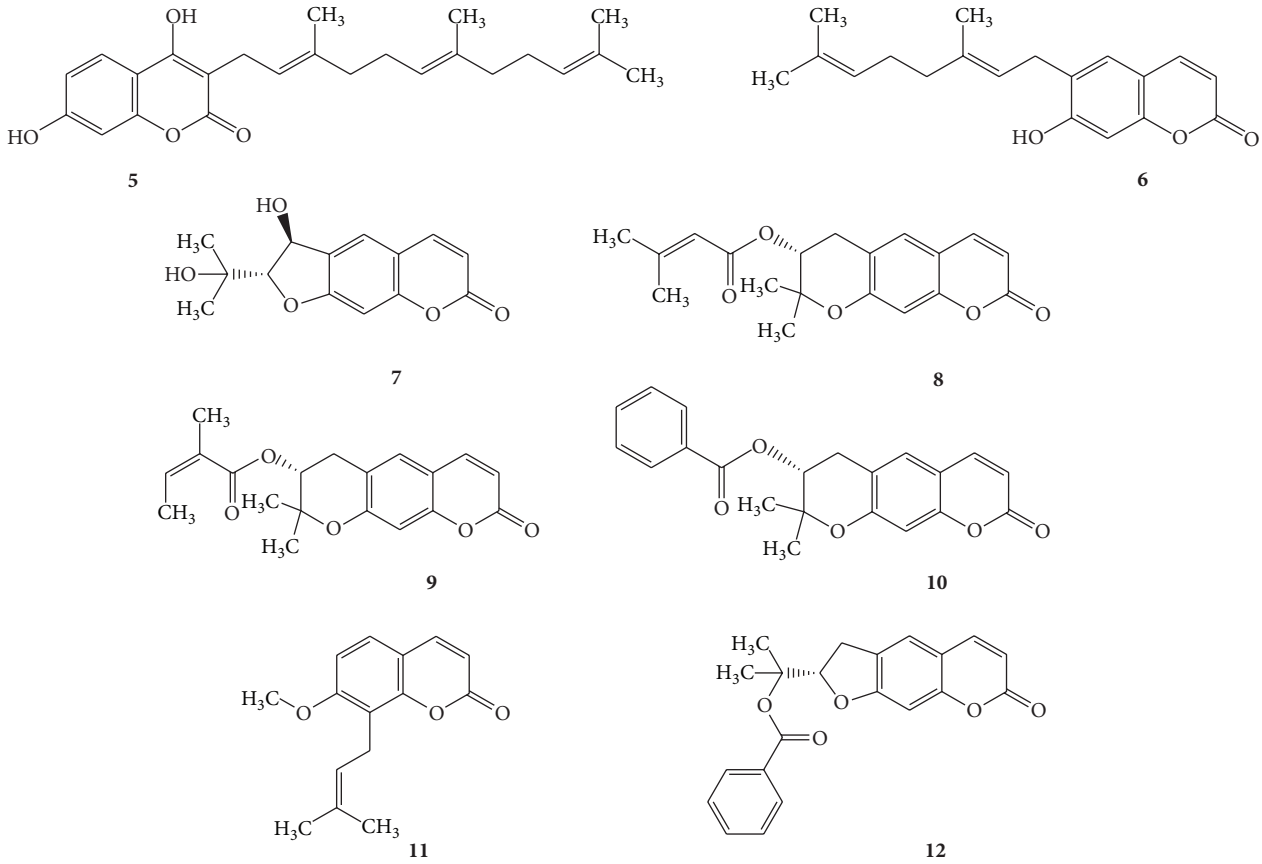


Figure 1: Coumarin analogue warfarin and vitamin K cycle.

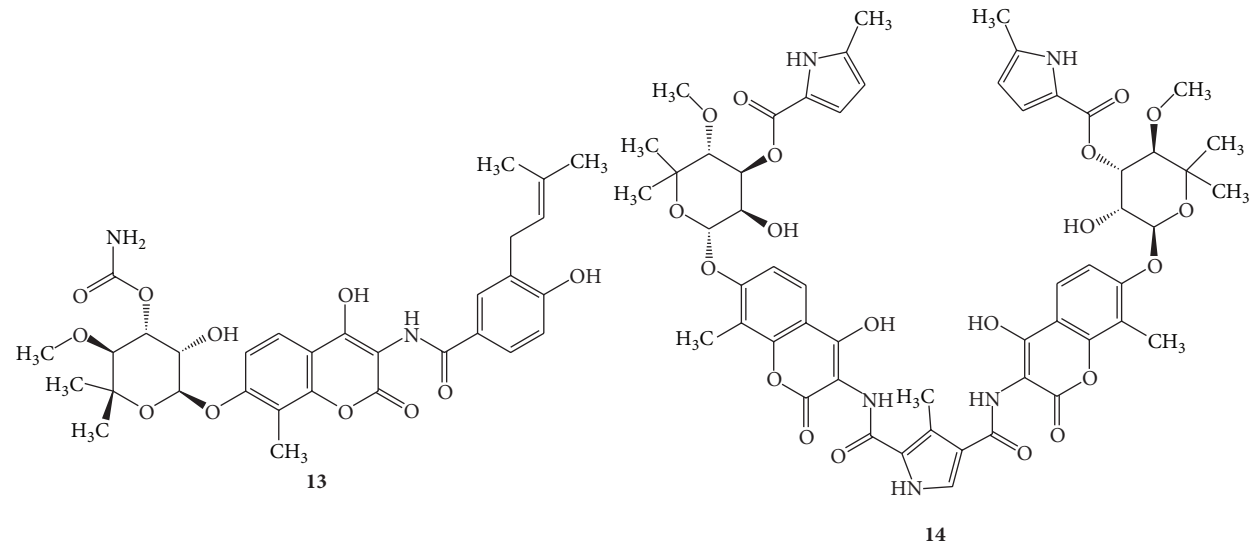
vitamin K conversion cycle, thereby causing hepatic production of partially carboxylated and decarboxylated proteins with reduced procoagulant activity [51, 52]. In addition to their anticoagulant effect, vitamin K antagonists inhibit carboxylation of the regulatory anticoagulant proteins C and S and therefore have the potential to exert a procoagulant effect. In the presence of calcium ions, carboxylation causes a conformational change in coagulation proteins [53–55] that promotes binding to cofactors on phospholipid surfaces. The carboxylation reaction requires the reduced form of vitamin K (vitamin KH_2), molecular oxygen, and carbon dioxide and is linked to the oxidation of vitamin KH_2 to vitamin K epoxide. Vitamin K epoxide is then recycled to vitamin KH_2 through two reductase steps. The first, which is sensitive to vitamin K antagonist [47, 49, 50], reduces vitamin K epoxide to vitamin K_1 (the natural food form of vitamin K_1), while the second, which is relatively insensitive to vitamin K antagonists, reduces vitamin K_1 to vitamin KH_2. Treatment with vitamin K antagonists leads to the depletion of vitamin KH_2, thereby limiting the γ-carboxylation of vitamin K-dependent coagulant proteins. The effect of coumarins can be counteracted by vitamin K_1 (either ingested in food or administered therapeutically) because the second reductase step is relatively insensitive to vitamin K antagonists (Figure 1). Patients treated with a large dose of vitamin K_1 can also become warfarin resistant for up to a week because vitamin K_1 accumulates in the liver and is available to the coumarin-insensitive reductase.

3.3. Coumarins for Antibacterial Activity. Coumarin (**1**) itself has a very low antibacterial activity, but compounds having long chain hydrocarbon substitutions such as ammoresinol (**5**) and ostruthin (**6**) show activity against a wide spectrum of Gram +ve bacteria such as *Bacillus megaterium*, *Micrococcus luteus*, *Micrococcus lysodeikticus*, and *Staphylococcus aureus* [19]. Another coumarin compound anthogenol (**7**) from green fruits of *Aegle marmelos* [3] shows activity against *Enterococcus*. Imperatorin (**2**), a furanocoumarin isolated from *Angelica dahurica* and *Angelica archangelica* (Umbelliferae) [56], shows activity against *Shigella dysenteriae* [57]. Grandivittin (**8**), agasyllin (**9**), aegelinol benzoate (**10**) and osthole (**11**) have been isolated from the roots of *Ferulago campestris* (Apiaceae) [32]. Felamidin (**12**) was also isolated from *Ferulago campestris* [6]. Aegelinol and agasyllin showed significant antibacterial activity against clinically isolated Gram-positive and Gram-negative bacterial strains such as *Staphylococcus aureus*, *Salmonella typhi*, *Enterobacter cloacae,* and *Enterobacter aerogenes*. Antibacterial activity was also found against *Helicobacter pylori* where a dose-dependent inhibition was shown between 5 and 25 mg/mL. (See Scheme 4.)

Many of the natural coumarins in existence have been isolated from higher plants; some of them have been discovered in microorganisms. The important coumarin members belonging to microbial sources are novobiocin, coumermycin, and chartreusin. Novobiocin (**13**) was isolated as fungal metabolite from *Streptomyces niveus* [58] and *Streptomyces spheroides* and has exhibited broad spectrum antibacterial activity against Gram-positive organisms such as *Corinebacterium diphtheria*, *Staphylococcus aureus*, *Streptomyces pneumoniae*, and *Streptomyces pyogenes* and Gram-negative organisms such as *Haemophillus influenzae*, *Neisseria meningitides,* and *Pasteurella* [21] and has shown DNA gyrase inhibition activity [22]. Coumermycin (**14**), that is, structurally similar to novobiocin is nearly 50 times more potent than novobiocin, against *Escherichia coli* and *Staphylococcus aureus*, but it produces a bacteriostatic action, and the organism developed resistance gradually. Coumermycin also



Scheme 4

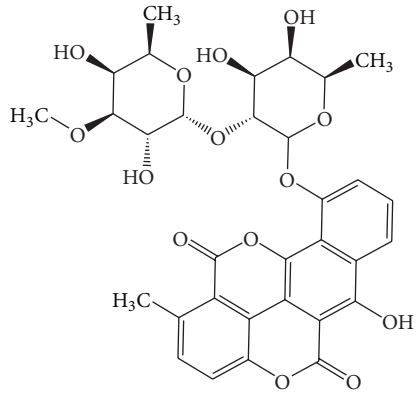


Scheme 5

inhibits the supercoiling of DNA catalyzed by *Escherichia coli* DNA gyrase [22]. (See Scheme 5.)

Chartreusin (**15**) was isolated from *Streptomyces chartreusis* and has an uncommon structure and was predominantly active against Gram-positive bacteria [38], but due to its toxicity, the compound has not been tried for therapeutic application. (See Scheme 6.)

3.4. Coumarins for Antifungal Activity. Osthole (**11**) is a bioactive coumarin derivative extracted from medicinal



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Scheme 6

plants such as *Angelica pubescens* [59], *Cnidium monnieri* [60], and *Peucedanum ostruthium* [61]. Osthole exhibited wide spectrum of antifungal activity against important plant pathogens such as *Rhizoctonia solani*, *Phytophtora capsici*, *Botrytis cinerea*, *Sclerotinia sclerotiorum,* and *Fusarium graminearum* [20]. A number of coumarins have been tested for antifungal activity, and the three most effective ones are psoralen (**16**) [11], imperatorin (**2**), and ostruthin (**6**). (See Scheme 7.)

3.5. Coumarins for Antiviral Activity. A large variety of natural products have been described as anti-HIV agents, and compounds having coumarin nucleus are among them. The inophyllums and calanolides represent novel HIV inhibitory coumarin derivatives. Inophyllum A (**17**), inophyllum B (**18**), inophyllum C (**19**), inophyllum E (**20**), inophyllum P (**21**), inophyllum G1 (**22**), and inophyllum G2 (**23**) were isolated from giant African snail, *Achatina fulica*. Inophyllums B and P (**18** and **21**) inhibited HIV reverse transcriptase (RT) with IC_{50} values of 38 and 130 nM, respectively, and both were active against HIV-1 in cell culture (IC_{50} of 1.4 and 1.6 μM) [33]. (See Scheme 8.)

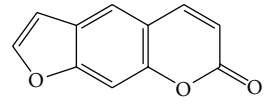
Two isomers, (+)-calanolide A (**24**) and (−)-calanolide B (**25**), have been isolated from the leaves of *Calophyllum lanigerum* (Clusiaceae). Calanolides A and B were completely protective against HIV-1 replication [34]. (+)-Calanolide A is a nonnucleoside RT inhibitor with potent activity against HIV-1. (−)-Calanolide B and (−)-dihydrocalanolide B (**26**) possess antiviral properties similar to those of (+)-calanolide A [35, 62]. Both (+)-calanolide A and (+)-dihydrocalanolide A (**27**) are stable at neutral pH and currently under development for the treatment of HIV infections. However, at a pH < 2.0 for 1 h, 73% of the (+)-calanolide A was converted to (+)-calanolide B while 83% of (+)-dihydrocalanolide A was converted to (+)-dihydrocalanolide B [35, 62]. Previously inophyllum A (**17**) and (−)-calanolide B (**25**) were isolated from the oil of seeds of *Calophyllum inophyllum* Linn and *Calophyllum cerasiferum* Vesque, respectively. Both of them belong to the family Clusiaceae and are known for potent HIV-1 RT inhibitors [5]. (See Scheme 9.)

Pyranocoumarins such as pseudocordatolide C (**28**) and calanolide F (**29**) were isolated from extracts of *Calophyllum lanigerum* var. austrocoriaceum and *Calophyllum teysmannii* var. inophylloide (King) P. F. Stevens (Clusiaceae). Both the compounds exhibited anti-HIV activity [36]. Imperatorin (**2**) also inhibits either vesicular stomatitis virus pseudotyped or gp160-enveloped recombinant HIV-1 infection in several T-cell lines and in HeLa cells [63]. (See Scheme 10.)

3.6. Coumarins for Anticancer Activity. Imperatorin (**2**) exhibited anticancer effects [64]. Osthole (**11**) is effective in inhibiting the migration and invasion of breast cancer cells by wound healing and transwell assays. Luciferase and zymography assays revealed that osthole effectively inhibits matrix metalloproteinase-s promoter and enzyme activity, which might be one of the causes that lead to the inhibition of migration and invasion by osthole [65]. Esculetin (**3**) exhibited antitumor activities [66] and rescues cultured primary neurons from *N*-methyl-D-aspartate toxicity [67]. Protective effects of fraxin (**30**) against cytotoxicity induced by hydrogen peroxide were examined in human umbilical vein endothelial cells [24]. Most of the coumarins grandivittin (**8**), agasyllin (**9**), aegelinol benzoate (**10**), and osthole (**11**) from *Ferulago campestris* plant exhibited marginally cytotoxic activity against the A549 lung cancer cell line [6]. Chartreusin (**15**) was shown to exhibit antitumor properties against murine L1210, P388 leukemias, and B16 melanoma [23]. 3″-Demethylchartreusin (**31**) is a novel antitumor antibiotic produced by *Streptomyces chartreusis* and it was a structural analogue of chartreusin containing the same aglycone of chartreusin, but different sugar moieties [38]. (See Scheme 11.)

Coumarin (**1**) which is isolated form cassia leaf oil exhibited cytotoxic activity [10].

3.7. Coumarins for Antihypertensive Activity. Dihydromammea C/OB (**32**) is a new coumarin that has been isolated from the seeds of the West African tree *Mammea africana* Sabine (Guttiferae) [68]. The molecular structure has been



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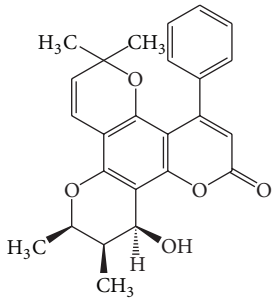
Scheme 7



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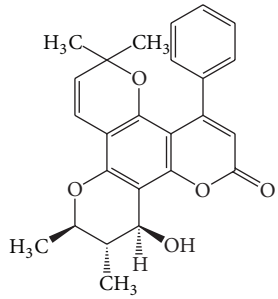

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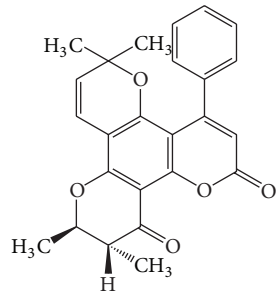

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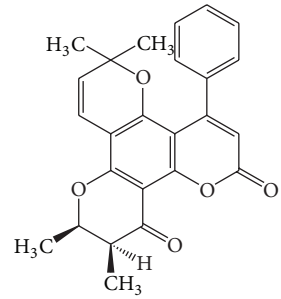

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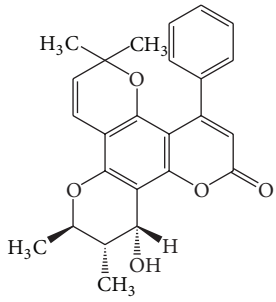

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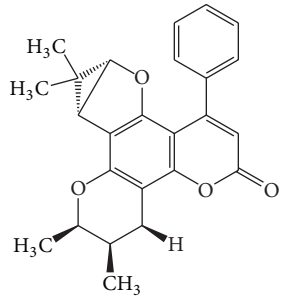

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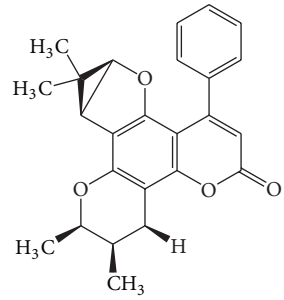

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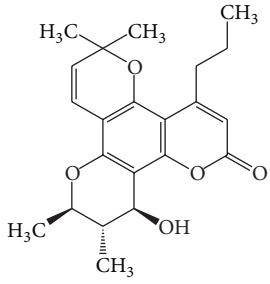
Scheme 8



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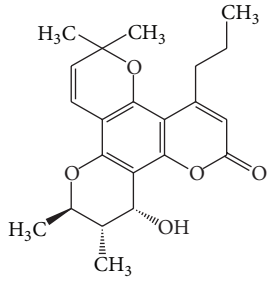

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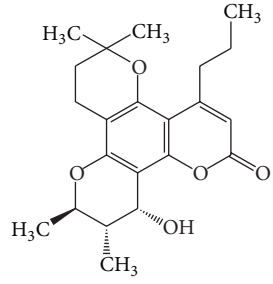

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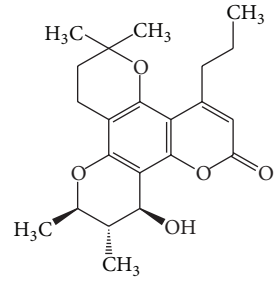

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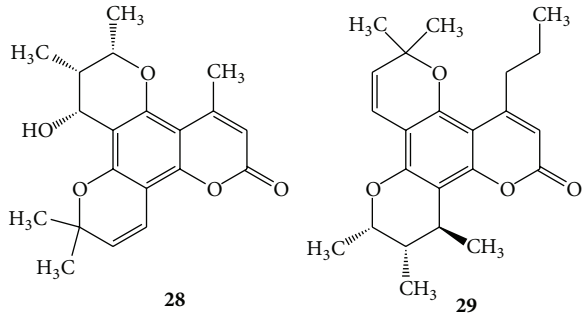
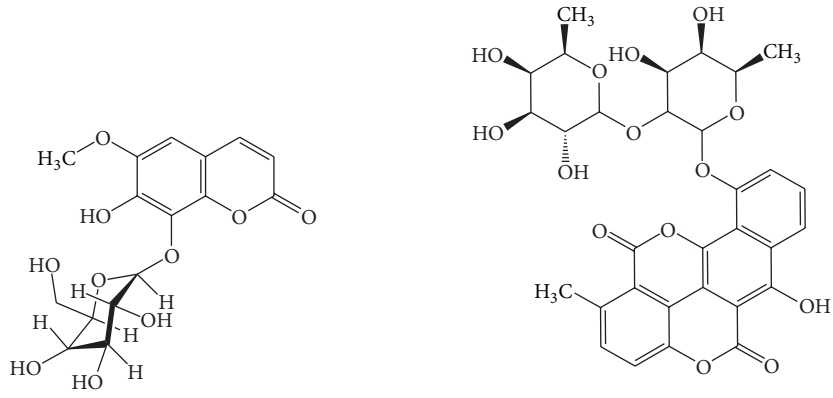
Scheme 9

elucidated by single crystal X-ray method [69]. Antihypertensive effects of the methanol and dichloromethane extracts of stem bark from *Mammea africana* in N^{ω}-nitro-L-arginine methyl ester induced hypertensive male albino Wistar rats weighing 250–300 g of 12–16-week old rats have been used in the studies [70]. Dichloromethane and methanol extracts of stem bark from *Mammea africana* exhibited a significant antihyperglycemic activity and improved the metabolic alterations in streptozotocin-induced male albino Wistar diabetic rats (3-month-olds, weighing 200–250 g) [71]. Vasodilatory effects of the coumarin are reported on cultured myocardial cells as well [72]. Scopoletin (**33**) was isolated form the fruits of *Tetrapleura tetraptera* TAUB (Mimosaceae) and it produces hypotension in laboratory animals *in vitro* and *in vivo* through its smooth muscle relaxant activity [4]. Visnadine (**34**), an active ingredient extracted from the fruit of *Ammi visnaga,* exhibited peripheral and coronary vasodilator activities and has been used for the treatment



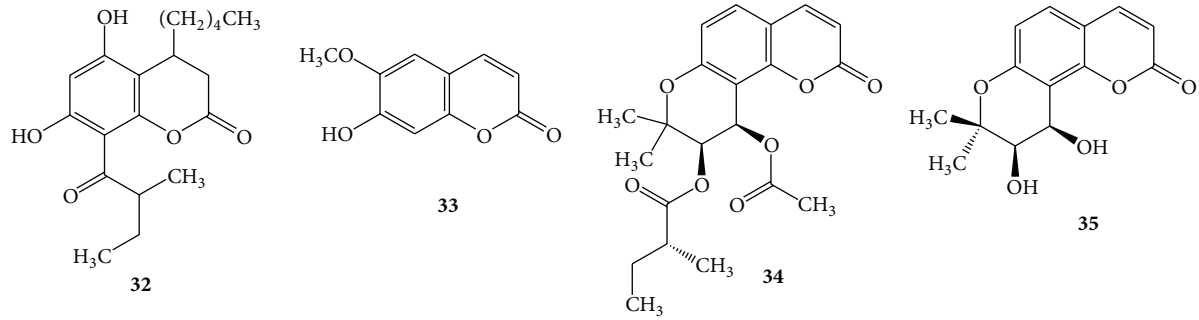
28 **29**

Scheme 10



30 **31**

Scheme 11



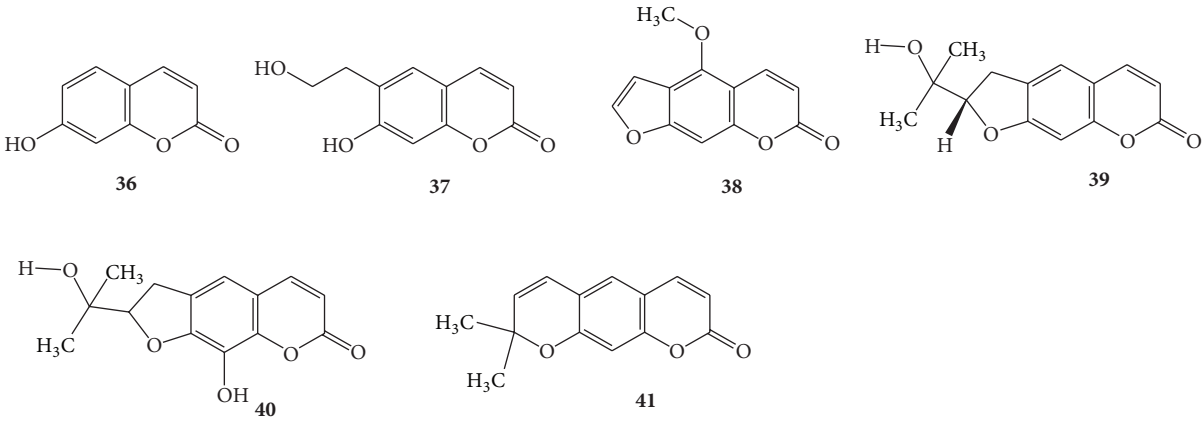
32 **33** **34** **35**

Scheme 12

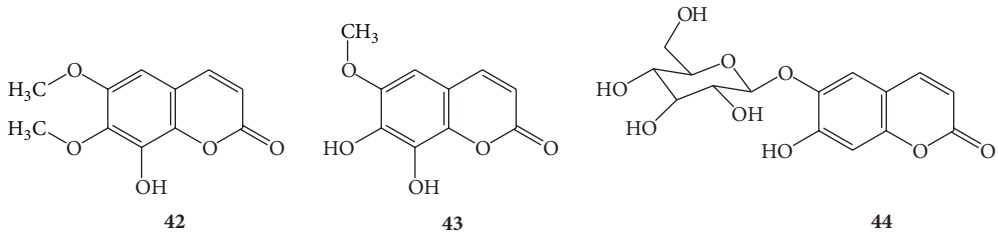
of angina pectoris [2]. Khellactone (**35**) was isolated from *Phlojodicarpus sibiricus* and it exhibited vasodilatory action [73]. (See Scheme 12.)

3.8. Coumarins for Antitubercular Activity. Umbelliferone (**36**) is found in many plants and obtained by the distillation of resins belonging to the natural order Umbelliferae [27]. Umbelliferone (**36**), phellodenol A (**37**), psoralen (**16**) and scopoletin (**33**), bergapten (**38**), (+)-(*S*)-marmesin (**39**), (+)-(*S*)-rutaretin (**40**), and xanthyletin (**41**) were isolated from the whole plants of *Fatoua pilosa*. The compounds scopoletin and umbelliferone are found to be active against *Mycobacterium tuberculosis* H_{37}Rv with MIC values of 42 and 58.3 μg/mL, respectively [25]. Compounds phellodenol A, (+)-(*S*)-marmesin and xanthyletin exhibited activity at 60 μg/mL and the remaining compounds exhibited activity at more than 119 μg/mL. Phellodenol A was also isolated from the leaves of *Phellodendron amurense* var. *wilsonii* [8]. (See Scheme 13.)

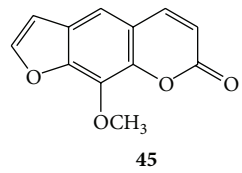
3.9. Coumarins for Anticonvulsant Activity. Imperatorin (**2**) showed anticonvulsant action in mice and the ED_{50} values ranged between 167 and 290 mg/kg. Acute neurotoxic effects in the chimney test revealed that the TD_{50} values for imperatorin ranged between 329 and 443 mg/kg [56]. Osthole (**11**) exhibited anticonvulsant action in mice and the ED_{50}



Scheme 13



Scheme 14



Scheme 15

values ranged between 253 and 639 mg/kg and the acute neurotoxic effects with the TD_{50} values ranged between 531 and 648 mg/kg [74].

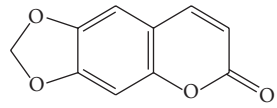
3.10. Coumarins for Multiple Sclerosis. Osthole (**11**) could be a potential therapeutic agent for the treatment of multiple sclerosis [75].

3.11. Coumarins for Antiadipogenic Activity. Fraxidin (**42**), [26] fraxetin (**43**), fraxin (**30**), esculetin (**3**), esculin (**44**), and scopoletin (**33**) have been isolated from the stem barks of *Fraxinus rhynchophylla* DENCE (Oleaceae). Esculetin (**3**) showed the most potent antiadipogenic activity against preadipocyte cell line, 3T3-L1 by *in vitro* assay system [27]. (See Scheme 14.)

3.12. Coumarins for Cytochrome P450 Inhibiting Activity. Methoxsalen (8-methoxypsoralen) (**45**) is found in the seeds of the *Ammi majus* (Umbelliferae) and exhibited potent mechanism-based microsomal P 450 inhibitor *in vitro* [76] and single-dose methoxsalen effects on human cytochrome P 450 2A6 activity [30]. (See Scheme 15.)

3.13. Coumarins for Antihyperglycemic Activity. Fraxidin (**42**) inhibited the formation of inducible nitric oxide synthase [77] and showed antihyperglycemic activity [78].

3.14. Coumarins for Antioxidant Activity. Fraxin (**30**) showed free radical scavenging effect at high concentration (0.5 mM) and cell protective effect against H_2O_2-mediated oxidative stress [24]. Esculetin (**3**) exhibited antioxidant property [79]. The antioxidant activity of the coumarins grandivittin (**8**), agasyllin (**9**), aegelinol benzoate (**10**), and osthol (**11**) was evaluated by their effects on human whole blood leukocytes and on isolated polymorphonucleated chemiluminescence [32]. Fraxin (**30**) and esculin (**44**) were characterized in stems and fruits of *Actinidia deliciosa* (kiwifruit) and *Actinidia chinensis* [80]. Fraxin (**30**) extracted from *Weigela florida* var. glabra leaves (Caprifoliaceae) protects cells from oxidative stress.



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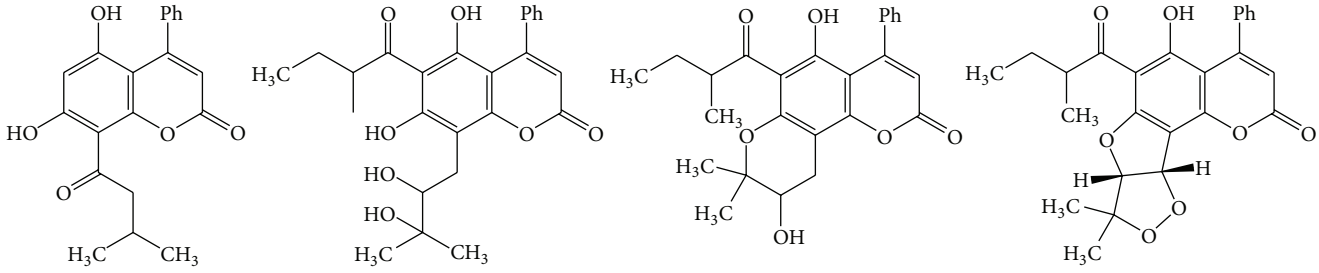
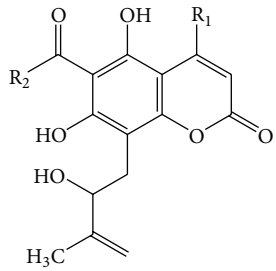
Scheme 16



47 **48** **49** **50**



51 R_1 = Ph, R_2 = $CH(CH_3)_2$
52 R_1 = *n*-Pr, R_2 = $CHCH_3CH_2CH_3$

Scheme 17

3.15. Coumarins for Neuroprotective Activity. Esculetin (**3**) also exhibited neuroprotective effects on cerebral ischemia/reperfusion injury in a middle cerebral artery occlusion model in mice at 20 μg/mL and was administered intracerebroventricularly at 30 min before ischemia [81].

3.16. Coumarins as Phytoalexins. Phytoalexins are oxygenated coumarin derivatives and they are produced in plants in response to fungal infection, physical damage, chemical injury, or a pathogenic process. The common property of phytoallexins is to inhibit or destroy the invading agents such as bacteria, insects, and viruses. Ayapin (**46**) is one among them and structurally it is 6,7-methylenedioxycoumarin. Initially it was isolated from *Eupatorium ayapana* (Asteraceae) [4]. Later, ayapin (**46**) was isolated from a number of other plants such as *Helianthus annuus* [8], *Artemisia apiacea* [2], *Pterocaulon virgatum* [14], and *Pterocaulon polystachyum* [15]. (See Scheme 16.)

4. Identification of Coumarins from Different Sources and Their Structural Elucidation

Coumarin compounds isodispar B (**47**), dispardiol B, (**48**), mammea A/AB cyclo E (**49**), mammea A/AB dioxalanocyclo F (**50**), disparinol D (**51**), and disparpropylinol B (**52**) have been isolated from the fruits and the stem bark of *Calophyllum dispar* (Clusiaceae) [37, 82, 83]. (See Scheme 17.)

Seed oil [5] and essential oils such as cinnamon bark oil [11] and lavender oil from roots (*Ferulago campestris*) [6], contain some amount of coumarin compound (**1**).

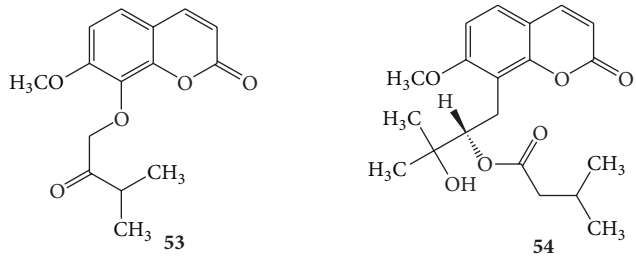
The main coumarin constituents found from the leaves of *Murraya paniculata* are 7-methoxy-8-(3-methyl-2-oxobutoxy)-2*H*-chromen-2-one (**53**) [7] and murrayatin (**54**). The latter was also found in the leaves of *Murraya exotica* [28]. (See Scheme 18.)

Prenylcoumarins (+)-fatouain A (**55**), (+)-fatouain A (**56**), (+)-fatouain C (**57**), (−)-fatouain D (**58**), (+)-fatouain E (**59**), and (−)-fatouain F (**60**), along with two new bis-prenylcoumarins, (+)-fatouain G (**58**), and (+)-fatouain H (**59**), have been isolated from the whole plants of *Fatoua pilosa* [84]. (See Scheme 19.)

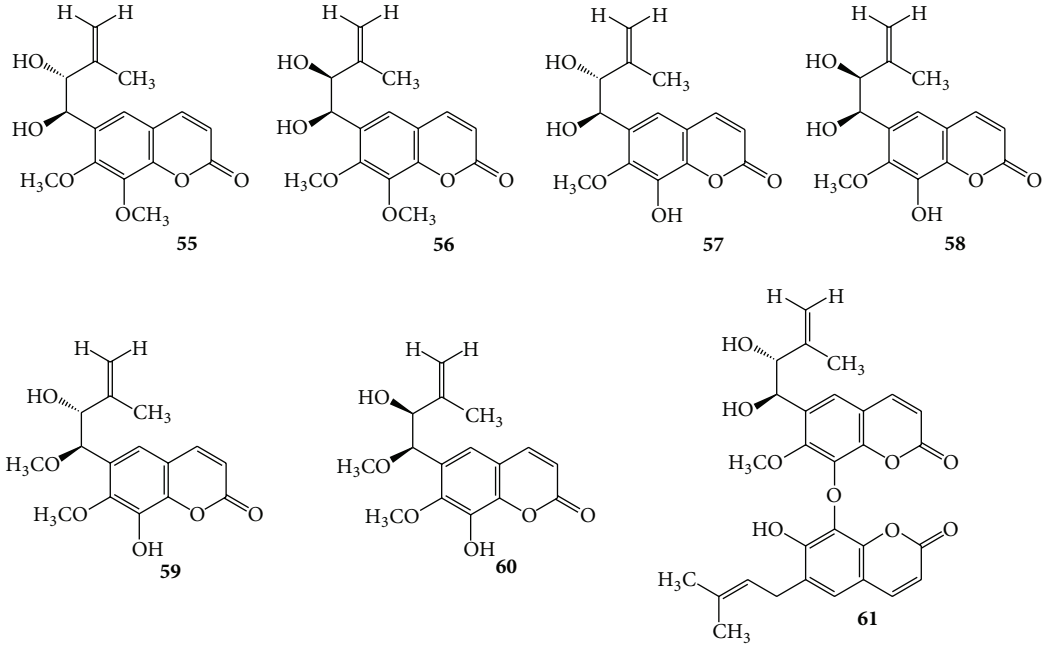
Marmin (**63**) is isolated from the bark. Imperatorin (**2**) and aurapten (**64**) are isolated from the fruit of *Aegle marmelos* (linn) Correa commonly known as Bael (or Bel) belonging to the family Rutaceae [29]. (See Scheme 20.)

5. Analysis of Coumarins by Different Methods

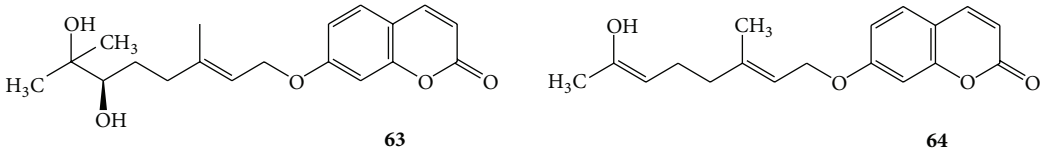
Various methods for the isolation and analysis of coumarins are chromatography (paper chromatography, thin layer chromatography, gas chromatography, and high-performance



Scheme 18



Scheme 19



Scheme 20

liquid chromatography), titrimetric and spectrophotometric (colorimetric and polarographic) methods. Methods for the analysis of coumarin derivatives stipulated by official pharmacopoeias (US Pharmacopoeia (23rd Edition), European Pharmacopoeia (3rd Edition, Suppl. 2001), and British Pharmacopoeia (16th Edition, 1998) and methods for coumarin determination in yellow sweet clover have been reviewed [85].

6. Conclusion

This paper covers natural coumarin lead compounds and their broad pharmacological properties and their methods of identification according to their official pharmacopoeias. Natural coumarins are of great interest due to their widespread pharmacological properties, and this attracts many medicinal chemists for further backbone derivatization and screening them as several novel therapeutic agents.

Acknowledgments

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