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REVIEW

Natural product coumarins: biological and pharmacological perspectives

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Abstract

Plants produce and release a vast variety of secondary metabolites with diversified functions, and possess ecological, toxicological and biological effects that mimic the activities of synthetic chemicals. Coumarins extracted from bacteria, fungi and many edible plants are widely used for their antibacterial, antifungal, antiviral, anti-HIV and anticancer activities. This review presents a concise summary based on the latest knowledge of the biological and pharmaceutical uses of coumarin and its derivatives, including an evaluation of future therapeutic potential. The presence of coumarins in various plant organs like fruits, seeds, roots, leaves and latex supplement recent work reported in scientific literature related to these compounds and their development. Due to low production in plants, the upscaling and industrial scale production, commercialization and industry demand of coumarins has faced hurdles. We searched Google Scholar and Web of Science for relevant literature upto 2018 using the keywords *pharmaceutical, biological activities* and *coumarins*. This review has thoroughly overviewed the related facts and figures about coumarins and its derivatives, especially in terms of biological and pharmaceutical properties including anti-microbial, anti-viral, anti-diabetic, anticoagulant, estrogenic, dermal photosensitizing, vasodilator, molluscacidal, antithelmintic, sedative and hypnotic, analgesic, hypothermic, anti-cancer activity, anti-oxidant, anti-parasitic, antihelmintic, anti-proliferative, anti-convulsant, anti-inflammatory, and anti-hypertensive activities. The pharmaceutical impact of coumarins on public health is a complex phenomenon, with several questions in relation to safety during medical therapies and consumption through diet. The present review focuses on coumarin clinical studies in the treatment of various chronic diseases such as cancer, diabetes, depression, Alzheimer's, Parkinson's and HIV. However, further research and review are necessary to broaden the therapeutic effectiveness of coumarin in patients suffering from such ailments.

Keywords Secondary metabolites · Multifunctionality · Antimicrobial activity · Pharmacopeia · Antibacterial

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Abbreviations

SMs	Secondary metabolites
DNA	83 Deoxyribonucleic acid
DM	Diabetes mellitus
IDF	International diabetes federation
WHO	World health organization
ROS	Reactive oxygen species
2-Ga	Gallium corrole-coumarin dyads
MIC	Minimum inhibitory concentration
HIV	Human immunodeficiency virus
DCK	Dicamphanoyl khellactone; PK2, Protein kinase 2

Introduction

Plants produce and release a vast variety of secondary metabolites (SMs) that have diversified roles in defending against bacteria, fungi, pests, insects, weeds and predators as well as being phytotoxic against herbivores (Rosenthal 1991; Hussain and Reigosa 2011, 2014a, b; Khalid et al. 2017; Hussain et al. 2015). Many SMs utilized as a lead compounds in herbicide discovery programs and the discovery of plant protection products. SMs are a novel group of plant-based chemicals that perform various functions and have ecological and toxicological modes of action that resemble synthetic pesticides (Tabanca et al. 2016). Plants employ different methods to cast secondary components inside their biochemical microenvironment through volatile emissions and breakdown of bark and foliate. Thus, SMs may change the rhizosphere chemistry (Singh et al. 2005) and consequently influence the uptake of essential plant nutrients as well as serve as natural toxins (Hawes et al. 2002). Although SMs serve protective functions against insects, pests and microbes, they also contribute to environmental protection (Bertin et al. 2003; Hussain and Reigosa 2016).

The biological responses of plants to SMs are sophisticated; they do not demonstrate an acclimation to biotic stress alone but are the result of the development of various distinct kinds of ecological communication and relations (Bertin et al. 2003; Hussain and Reigosa 2014a, 2014b; Khalid et al. 2017). Although these compounds alter the growth and productivity of plants through biological reactions, there are thousands of different metabolites (particularly phenolics, flavonoids, alkaloids and terpenoids) with a wide range of toxicity (Hussain and Reigosa 2011). The behavior of SMs can be distinct in accordance with their respective structures. Membrane disorders have speculated to result from SM actions, though recent studies do not support this idea (Inderjit 1996).

Biological and pharmaceutical studies have focused on obtaining data related to the interaction between different chemical materials and plants via SMs. Coumarins have utilized for different industrial purposes such as fragrances and skin treatment products (Egan et al. 1990a, b). Several vegetations like grasses, cereals and medicinal plants have demonstrated different concentrations of coumarins. The synthesis of coumarins mainly occurs in fruits while other plant parts like roots, leaves and stems have varying levels. Various authors have documented the importance of coumarins and studies examining clatogenic and phytochemical behavior have proven the phytochemical activity of these substances (Guardado et al. 2017; Yasameen et al. 2017; Venugopala et al. 2013; Venugopala et al. 2013). However, the phytotoxic effects of different coumarin and coumarin derivatives are unclear with concerns over safety in medical therapies and consumption through diet.

The effects of coumarin exposure on human health are complex, and several questions remain unsolved in terms of their medical therapeutical potential, pharmacology and consumption through diet. The present article will review what is currently known in the literature regarding the biological and pharmaceutical activities of the coumarin family (coumarin and coumarin derivatives), plant sources of coumarins as well as the therapeutic health impact of coumarin exposure. Furthermore, we have summarized a list of plants that possess coumarins in various plant organs such as leaves, stems, roots, bark, seeds, flowers and fruits.

Distribution of coumarin among plant organs

Various natural products and plant-based medicinal compounds have demonstrated excellent therapeutic efficacy against human infections and metabolic disorders (Newman and Cragg 2012). These include SMs produced in certain plant species following disease, the wilting process, drying as well as other environmental stresses. Some coumarins (furacoumarins) may inhibit plant metabolism via inhibition of root tip and seed germination (Weinmann 1997). Figure 1 demonstrates some of the important medicinal plants that exhibit coumarins. Moreover, coumarins can be present in different plant organs such as leaves, roots, stems and flowers. Furanocoumarins have demonstrated in fruits (*Pastinaca sativa*) and leaves (*Anglica archangelica*) respectively (Walker et al. 2003; Zangerl et al. 1989). However, simple coumarin (osthenol) have reported in plant roots (Zobel and Brown 1991). Coumarin concentrations have been examined in various plants and range from <1 mg/kg in celery, 7000 mg/kg in cinnamon and up to 87,000 mg/kg in cassia (Lake 1999). Abraham et al. (2010) also documented coumarin levels of 1500 mg/kg in cassia powder and <1000 mg/kg in cassia sticks.

Coumarins have been found to accumulate more in the seed coats and oil tubes of fruits, e.g. in *Pastinaca sativa* (Zobel and Brown 1991) in comparison to other plant organs. The authors also documented that significantly higher concentrations of coumarins were present in *Heracleum lanatum* seeds and in *A. archangelica* with the quantity less in fruit tissues. Some plant species excrete coumarins on their leaf surface. Studies have demonstrated that coumarins also play a characteristic role in plant defence strategies, have higher concentrations in spring versus autumn leaves, and that younger leaves possess more coumarins than older leaves (Zobel and Brown 1989, 1990, 1991). This phenomenon is particularly apparent in several plant species including *Pimpinella anisum, Psoralea bituminosa, Pastinaca sativa, Apium graveolens, Heracleum lanatum,* and *Ferula communis, var. glauca* (Zobel and Brown 1990).

Coumarins also serve as natural flavoring and as a perfuming agent in their natural state in *Cinnamomum cassica, Anthoxanthum odoratum* and *Dipteryx* odorata (Leal et al.

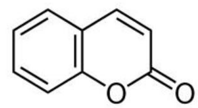
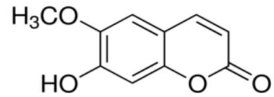
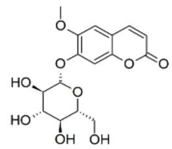
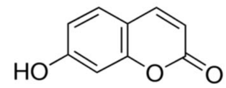
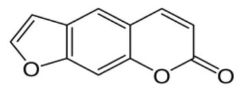
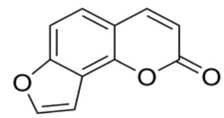
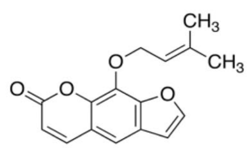
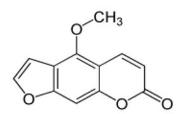
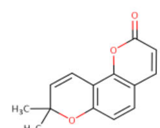
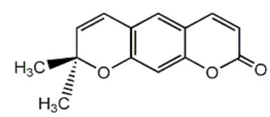
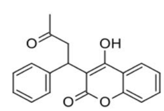
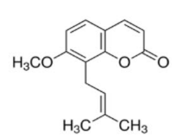
Fig. 1 Some important medicinal plants that contain coumarins; *Artemisia keiskeana* (**a**), *Mallotus resinosus* (**b**), *Jatropha integerrima* (**c**), *Ferula tingitana* (**d**), *Zanthoxylum schinifolium* (**e**), *Phebalium clavatum* (**f**), *Mammea siamensis* (**g**).

2000). Coumarin content varied significantly in dry cinnamon and was observed in the range of 9900 – 12180 mg/kg (He et al. 2005; Woehrlin et al. 2010) as well as 5 – 7670 mg/kg in ground cinnamon (Lungarini et al. 2008). Surangin B, surangin C, mammea E/BB and mammea E/BC are active coumarins reported in *M. siamensis* (Issakul et al. 2004). Cinnamon bark oil and cassia leaf oil demonstrated significant presence of coumarins in the range of 7000 and 87300 ppm respectively, while lavender oil has also shown to possess coumarins (Mahidol et al. 2002). Coumarins were also present in green tea, chicory, cloudberry and bilberry (Lake 1999). Surangin A and surangin B were reported in *Mammea longifolia* (Wight) Planch and Triana, (Joshi et al. 1969). Trumble et al. (1992) documented that bergapten levels in *Apium graveolens* varied from leaf to petiole. Moreover, a seasonal trend was observed as bergapten concentrations increased during the seedling stage while decreasing at maturity. Older parsley leaves also constitute furanocoumarins-specific bergaptol-*O*-methyltransferases (Lois and Hahlbrock 1992).

Coumarins are widely distributed in many plant species and have a wide range of biochemical and pharmaceutical phytotoxicity (Harada et al. 2010). Mostly coumarins were reported from Rutaceae and Umbelliferae family plant species. The quantity of coumarin in different plant organs varies with maximal percentage reported in fruits followed by roots, stems and leaves (Lake 1999). Jung et al. (2012) showed the presence of various coumarins such as scopolin, scoparone, esculetin, scopoletin, umbelliferone and isoscopolin in the medicinal plant *Artemisia capillaris*. Coumarins such as novobiocin and coumermycin were isolated from *Streptomyces* while aflatoxins were identified in *Aspergillus* species (Cooke et al. 1997; Cooke and Kennedy, 1999). Aflatoxins are fungal metabolites that may be highly toxic, with Aflatoxin B1 being the most commonly occurring member of this group (Cooke and Kennedy 1999). Antibiotics of the coumarin group are potential inhibitors of Deoxyribonucleic acid (DNA) gyrase, e.g. novobiocin, coumermycin A1 and clorobiocin. These can be obtained from different *Streptomyces* species and possess a 3-amino-4-hydroxy-coumarin moiety (Chlorobiocin, Coumermycin A1) (Chen and Walsh 2001). Coumarins are widely distributed in many plant species and have a wide range of biochemical and pharmaceutical phytotoxicities (Harada et al. 2010) (Table 1).

Coumarins were reported in different plant organs but the quantity of specific furanocoumarins varies according to enzyme activity in plant phytotoxic mechanisms. Diawara et al. (1995) isolated several coumarins from celery (*Apium graveolens* L. var. *dulce* Miller) leaves. In celery seeds,

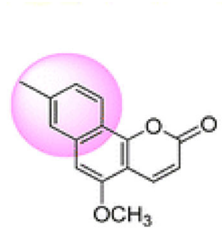
Table 1 Different coumarin and their derivatives having different structure features and functional characteristics

Classification	Features	Examples	
Simple coumarins	Hydroxylated, alkoxylated or alkylated on benzene ring	 Coumarin	 Scopoletin
		 Scopolin	 Umbelliferone
Furanocoumarins	Furan ring attached to benzene ring. Linear or Angular	 Psoralen	 Angelicin
		 Imperatorin	 Bergapten
Pyranocoumarins	Pyran ring attached to benzene ring. Linear or Angular	 Seselin	 Xanthyletin
Pvrone-substituted	Substitution on pyrone ring, often at 3-C or 4-C position	 Warfarin	
Minor Coumarin		 Osthole	

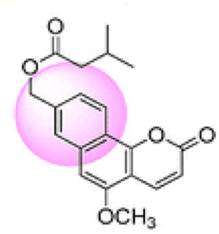
furanocoumarins are restricted to schizogenous canals (Berenbaum et al. 1991) and accumulate primarily in petiolar and foliar canals in cow parsnip or *Heracleum lanatum* Michx (Apiaceae). Higher levels of furanocoumarin has reported from field-grown plants in comparison to laboratory or glasshouse yields (Diawara et al. 1995). Milesi et al. (n.d.) studied the phytochemical constituents of *Ruta graveolens* and isolated furanocoumarins from the leaves and stems of this plant. Table 2 shows a list of plants and plant parts containing coumarin.

Table 1 (continued)

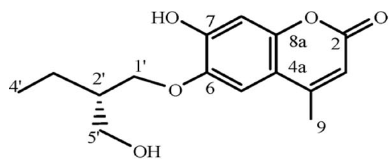
Other coumarin & their derivatives



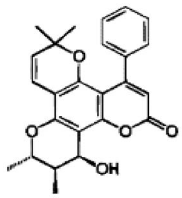
Muralatins A



Muralatins B

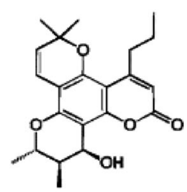


Pavietin



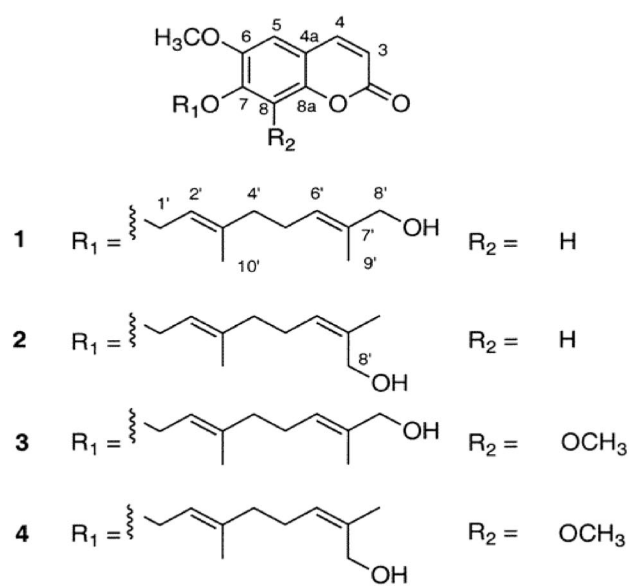
1

Soulattrolide



2

Costatolide



Artekeiskeanols A–D (**1**–**4**)

Table 2 Name of the plants and parts of plant containing Coumarin

Plant Species	Plant Parts	References
Murraya alata l	leaves	Lv et al. 2015a, b
Peucedanum ostruthium (L.) Koch	rhizomes	Vogl et al. 2011
Artemisia keiskeana	whole plant	Kwak et al. 2001
Aesculus pavia l	leaves	Curini et al. 2006
Mallotus resinosus	roots	Shannon et al. 2004
Jatropha integerrima	roots	Sutthivaiyakit et al. 2009
Pterocaulon virgatum w	whole plant	Debenedetti et al. 1994
Ferula tingitana	roots	Miski et al. 1985
Eriostemon spp.	Aerial parts	Sarkar et al. 1995
Aegopodium podagraria L.	roots	Fischer and Svendsen 1976
Angelica archangelica L.	roots	Fischer and Svendsen 1976
Levisticum officinale (Hill) Koch	roots	Fischer and Svendsen 1976
Peucedanum palustre (L.) Moench	roots	Fischer and Svendsen 1976
Angelica archangelica L.	roots	Harmala et al. 1991, 1992
Artemisia incanescens	roots	Marco et al. 1987
Seselitortuosum A	Aerial parts	Ceccherelli et al. 1989
Micrandra elata	roots	Borris et al. 1980
Artemisia spp.	roots	Greger et al. 1982
Microcybe multiflorus & Nematolepis	Aerial parts	Hassan et al. 2016
Calophyllum teysmannii	latex	Pengsuparp et al. 1996
Phebalium clavatum	Aerial parts	Colombain et al. 2002
Opopanax chironium		Appendino et al. 2004
Mammea siamensis	flowers	Mahidol et al. 2002
Phellodendron amurense var. wilsonii	leaves	Wu et al. 2003a, b
Clausena lansium	roots	Shen et al. 2014
Streptomyces spp.	Aerial parts	Cheenpracha et al. 2010
Tetradium glabrifolium	stem bark, roots	Ng et al. 1987
Stauranthus perforatus	roots	Macias et al. 1999
Soymida febrifuga	bark	Awale et al. 2009
Leucaena leucocephala	Fruit, seeds	Babayemi et al. 2004a, b
Gliricidia sepium	Fruit	Babayemi et al. 2006
Ferula pseudalliacea	roots	Dastan et al. 2014
Zanthoxylum bungeanum	Bark	Yang 2008; Chang et al. 1997
Biebersteinia multifida	roots	Monsef-Esfahani et al. 2013
Loeselia mexicana	whole plant	Navarro-García et al. 2007
Calophyllu dispar	Fruits, stem bark	Guilet et al. 2001
Ferula Spps.	roots	Ahmad 1999; Ahmad et al. 2001, Iranshahi et al. 2004a, 2004b, Iranshahi et al. 2007, Iranshahi et al. 2008, Mehrdad et al. 2010, Chen et al. 2000,
Zanthoxylum schinifolium	Bark, fruits, leaves, stem	Jo et al. 2002, Chen et al. 1995, Li et al. 2013, Tsai et al. 2000, Chang et al. 1997, O'Leary et al. 2016; Cheng et al. 2002, Min et al. 2011, Fang et al. 2010
Zanthoxylum americanum	Whole plant	Ju et al.
Xeromphis uliginosa	bark	Nagaiah et al. 1992
Artemisia carvifolia	bark	Harayama et al. 1994
Morus alba	bark	Piao et al. 2009

Abiotic factors that govern coumarin levels in plants

SM synthesis and their accumulation in plants is regulated in space and time (Wink and Schimmer 1999a, b) by abiotic environmental factors, including light intensity, minerals in soil, osmotic stress, drought, salinity, and seasonality (Hussain et al. 2011; Hussain and Reigosa 2011, 2014a, b; Dayan et al. 2009). In fact, abiotic environmental factors that restrict the production of SM indirectly control the relations of plants with their biotic environment (Hussain and Reigosa 2014a, b). Therefore, to understand the function of coumarin as a moderator of biotic interactions, it is important to investigate how its synthesis is affected by abiotic factors. Scopoletin and its conjugated derivative scopolin are simple 7-hydroxylated coumarins found in a variety of fungi and a range of botanical families, notably cereals, *Compositae,* legumes and Solanacae (Kai et al. 2006).

Scopoletin and ayapin are phytoalexins found in sunflower (Tal and Robeson 1986). Other researchers reported the presence of scopoletin in leaf leachates and ayapin from sunflower plants infected with broomrape (Jorrin et al. 1996). In 2006, Yang and his co-workers demonstrated the presence of 39 coumarins in *M. Americana*. Studies indicate that coumarin levels vary in different plant organs depending on the growth period. *Ruta graveolens* L. Several secondary metabolities such as coumarins, alkaloids, terpenes and flavonoids have reported from family Rutaceae (Kostova et al. 1999). Yang et al. (2006) revealed the presence of coumarin in *Dendrobium thyrsiflorum* Rchb. f. (Orchidaceae) at the flowering stage. Furanocoumarins are mostly present in celery, parsnip and parsley and become highly active phytotocic compounds following exposure to UV-A radiations (Rice 1984). In 2008, Kalkhambkar displayed the excellent analgesic properties of fluorinated coumarins while 1-azo coumarins demonstrated moderate actions in this area. Different coumarin were also isolated from leaf, fruit and root oils in *Ruta graveolens* and the aerial parts of *R. graveolens* (De Feo et al. 2002).

Biological activities of coumarins and use in pharmaceutical industry

Coumarins are phytochemicals that possess several biological and therapeutic properties such as anti-microbial, anti-viral (Hassan et al. 2016), anti-diabetic (Pari et al. 2014), anti-coagulant, (Xu et al. 2015a, b) estrogenic, dermal photosensitizing, vasodilator, molluscacidal, sedative and hypnotic, analgesic, hypothermic (Yamahara et al. 1989a, b), and anti-cancer (Thakur et al. 2015; Dandriyal et al. 2016) characteristics. Furthermore, anti-oxidant, anti-parasitic, anti-helmintic, anti-proliferative, anti-convulsant, anti-inflammatory (Wanga et al. 2017), and anti-hypertensive activities (Yamahara et al. 1989a, b; Tandan et al. 1990; Kayser and Kolodziej 1999) of several coumarins have also studies by several researchers and summarized in Table 3.

Anti-diabetes activity

Diabetes mellitus (DM) is a serious problematic disease characterized by abnormally high levels of glucose in the blood (hyperglycemia) (http 1). In the end, DM can lead to damage of a number of body organs such as nerves, kidneys and blood vessels (http 2). According to recent reports from the International Diabetes Federation (IDF), approximately 415 million people globally were diagnosed with DM in 2015, with this figure expected to increase to 642 million by 2040 (http 3). According to the World Health Organization (WHO), DM will be the seventh leading cause of death globally, with South-East Asian, African and Eastern Mediterranean countries largely affected (http 1).

Three different types of diabetes have been reported; Type 1 diabetes, type 2 diabetes and gestational diabetes (Kuzuya and Matsuda 1997). When the pancreas fails to excrete sufficient insulin due to disturbaces in metabolic processes, the primary symptoms of Type 1 diabetes result. However, Type 2 diabetes has several consequences, which include augmented hepatic glucose production, abnormal islet β-cell function, incretin system abnormalities and insulin resistance of peripheral tissues (Holst et al. 2009; Khan et al. 2013). A patient suffering from type 2 DM may suffer from severe damage to the heart, eyes and kidneys (Kumar and Verma 2011). Because of its complexities, diabetes is a notorious sickness and a major cause of human death following (1) cancer, (2) cardiovascular diseases and (3) cerebrovascular diseases. Isofraxidin (7-hydroxy-6,8-dimethoxycoumarins) has shown to be effective against type 2 DM in mice, inducing hypoglycemic and hypolipidemic changes (Niu et al. 2012). Other coumarins such as umbelliferone, esculentin and osthole have shown promising therapeutic effects on diabetes. The repairing pancreatic β-cell and insulin production enhancement might help to reduce the complexities of diabetes (Kang et al. 2014; Islam et al. 2013). Several coumarin molecules in combination with metal ions have shown that these complexes are useful in the treatment of diabetes, cancer and other bacterial infections (Grazul and Budzisz 2009). Cinnamomulactone, coumarins and *trans*-cinnamic acid have demonstrated inhibitory activity against both gastritis and diabetes (Kim et al. 2017).

Wang et al. (2013) employed coumarins (extracted from *Urtica dentate*) for antidiabetic evaluation against 8-week old mice. They reported a significant reduction in insulitis, improved pancreatic islet number and inhibition of the diabetes by 26 weeks in comparison to the untreated group. In another study, Pari et al. (2014) induced type 2 diabetes in rats via streptoziticin nicotinamide. The authors administered oral treatment of coumarins in afflicted animals and found a marked antilipidemic effect against diabetes mellitus. Coumarins impeded the damage to pancreatic β-cell (Li et al. 2017). Ali et al. (2018) concluded that coumarins significantly decreased human recombinant aldose reductase (HRAR).

The 4,5-di-O-caffeoylquinic acid, umbelliferone, esculetin, esculin and scopoletin were extracted from *Artemisia capillaris* and demonstrated therapeutic and preventive capacity against diabetes (Jung et al. 2012). Morphological features like swelling, vacuolation and liquefaction of lens fibers were inhibited via

Table 3 Pharmacological and biological activities of Coumarin

Activity	References
Antibacterial	Bisignano et al. 2000; De-Souza et al. 2005
Antibacterial & antifungal	Carlos et al. 2006
Antifungal	Shukla et al. 1999
//	Sardari et al. 1999
//	Kwon et al. 2005
Antimicrobial	Kawase et al. 2001
Anti-inflammatory activity, in vitro, in vivo	Fylaktakidou et al. 2004; Okada et al. (1995); Lino et al. (1997);
	Hiermann and Schantl (1998); Hsiao et al. (1998); Rocha and Silva (1991); More and Mahulikar (2011); Garcia-Argaez et al. (2000); Roos et al. (1997); Leal et al. (2000), Cao et al. 2009; Siddiqui et al. 2010; Kalkhambkar et al. 2007; Selim and Ouf 2011.
	Bahadır et al. 2011; Bansal et al. 2009; Bhagwat 2009; Dinarello 2010; Gacche et al. 2003; Gate et al. 2003; Hadjipavlou-Litina et al. 2007; Kalkhambkar et al. 2011; Kang et al. 2009; Khan et al. 2010; Kontogiorgis et al. 2006; Menghini et al. 2010; Pan et al. 2010; Pozharitskaya et al. 2010; Sandhya et al. 2011; Sashidhara et al. 2011; Symeonidis et al. 2009; Timonen et al. 2011; Upadhyay et al. 2011; Zhao et al. 2012; Sandhu et al. 2014; Chitte et al. 2016; Kirsch et al. 2016.
Antimicrobial activity	Ajani and Nwinyi (2010); Martínez-Palou (2007); Naik and Desai (2006); Moghaddam et al. 2009; Siddiqui et al. 2010; Zavrsnik et al. 2011
	Patel et al. 2010; Porwal et al. 2009; Chimenti et al. 2006;
	Mulwad and Satwe 2006; Kusanur and Kulkarni 2005; Gupta and Phull 1996; Gupta and Prabhu 1996, Kadhum et al. 2011, Al-Amiery et al. 2012, Gottlieb et al. 1979
Antifungal activity	Siddiqui et al. 2010; Naik and Desai 2006
	Gottlieb et al. 1979; Delle et al. 1995; Cuca-Suarez et al. 1998; Compagnone et al. 1993
	Trani et al. 1997; Trani et al. 2004; Torres et al. 1979; Rahman 2000; Brooker et al. 2007.
	Al-Barwani and ElTayeb 2004; Prats et al. 2007,
Antimalarial activity, in vitro, in vivo	Siddiqui et al. 2010; Naik and Desai 2006
Antitumor/anti-cancer activity, in vitro	Okuyama et al. (1990); Mizuno et al. (1994); Satyanarayana et al. 2008
	Seliger (1997); Kofinas et al. (1998); Fujioka et al. (1999), Rita et al. 2004
	Bronikowska et al. 2012; Ma et al. 2012, Chen et al. 2012; Gacche and Jadhav 2012
	Desai et al. 2008; Min et al. 2011; Siddiqui et al. 2010; Lv et al. (2017); Dandriyal et al. (2016); Rajabi et al. (2015); Paul et al. (2013); Kamath et al. (2015); Zhang et al. 2014; Amin et al. 2014; Bertin et al. 2014; Iranshahi et al. 2015; Hamulakova et al. 2016; Kavetsou et al. 2017;
Antidiabetic	Wang et al. (2013); Pari et al. (2014);
	Pari and Rajarajeswari (2010); Niu et al. 2012
	Marshall et al. 1991; Dighe et al. 2010; Budzisz et al. 2003; Reddy et al. 2004; Musa et al. 2008; Kawase et al. 2001,
	Ali et al. 2015; Ali et al. 2016a, 2016b; Chang et al. 2015; Ishita et al. 2016; Jung et al. 2017; Kato et al. 2010; Kim et al. 2013;
Antiviral activity, in vitro	Fuller et al. (1994); More and Mahulikar 2011; Naik and Desai (2006); Siddiqui et al. 2010
Calcium antagonistic activity, in vitro, in vivo	Vuorela (1988); Yamahara et al. (1989a, 1989b); Törnquist and Vuorela (1990)
Cytostatic effect, in vivo	Egan et al. (1997), Al-Amiery et al. 2012,
Anticoagulant activity	Nikhil et al. 2012; Venkataraman et al. 2014; Egan et al. 1990a, b; Naik and Desai 2006; Goodman and Gilman 2006; Bubols et al. 2013;
Anti-oxident activity	Singh et al. 2010; Melagraki et al. 2009; Stanchev et al. 2009, Kadhum et al. 2011; Al-Amiery et al. 2012;
Anticonvulsant Activity	Siddiqui et al. 2009; Al-Majedy et al. 2016;
Antihyperlipidemic Activity	Sashidhara et al. 2010; Najmanova et al. 2015;
Tyrosinase Inhibitor Activity	Fais et al. 2009
Anti-parkinsonism Activity	Matos et al. 2009
Phototoxic activity	Cadet et al. 1990; Dall'Acqua et al., 1970, 1972, 1979; Goyal and Grossweiner 1979; Grube et al. 1977; Ley et al. 1977; Musajo and Rodighiero 1972; Rodighiero and Dall'Acqua 1976; Veronese et al. 1979; Melough et al. 2017a, 2017b; Lee et al. 2016; Cancalon et al. 2011; Fidel et al. 2016; Chaudhary et al. 2015; Chaudhary et al. 2014; Xu et al. 2015a, b; Chebrolu et al. 2016; Girennavar 2007; Kakar et al. 2004; Goosen et al. 2004; Bailey et al. 2003; Guo et al. 2000; Gorgus et al. 2010; Widmer and Haun 2005; Messer et al. 2011; Lin et al. 2009; Uckoo et al. 2012; Melough et al. 2017a; Ceska et al. 1986.

aldose reductase in GAL rats following treatment with esculetin (Kim et al. 2016). Gambier drinks (aqueous extract: 100, 200 and 300 mg/kg) through oral administration decreased hypoglycemic activity and blood glucose level in alloxan-induced mice (Zebua et al. 2018).

Anti-inflammatory activity

Inflammation represents biological processes that occur following physical, chemical and biological stimulation of cells (Khan et al. 2005). Several coumarins such as umbelliferone, scopoletin, columbiatnetin, visniadin and marmin have shown significant anti-inflammatory potential (Table 4) (Bansal et al. 2013). Lino et al. (1997) studied the involved mechanisms of action, production and release of bradykinins, histamines, prostaglandins and serotonin. The phytotoxic potential of coumarin demonstrated non-steroidal anti-inflammatory drug-like action. Coumarins also used for treating scalds through the removal of extravasated protein (Piller 1997). Alami et al. (1999) documented that the octadecanoic pathway was inhibited through the joint actions of scopoletin and umbelliferone (Table 5).

Several authors have reported that the generation of reactive oxygen species (ROS) and free radical-mediated injury leads to the development of severe chronic diseases such as tissue edema and inflammation. Natural phytotoxins such as coumarin compounds have demonstrated the scavenging activity of oxgen molecules (Fylaktakidou et al. 2004). Melagraki et al. (2009) designed synthesized and tested coumarin-3-carboxamides and their hybrids and showed that they possessed in vitro lipoxygenase and in vivo anti-inflammatory activity. Heraclenin, seselin, psoralen, imperatorin, skimmianine and heraclenol were reported in the aerial parts of *Decatropis bicolor* (Garcia-Argaez et al. 2000). The authors concluded that all the compounds showed anti-inflammatory activity against ear edema in mice. Ghate et al. (2005) also found that benzofuranyl coumarins had anti-inflamatory properties. Iranshahi et al. (2009) discovered that umbelliprenin had invivo anti-inflammatory activity and inhibited carrageenin-induced paw edema significantly (39 %).

Phototoxicity

Many coumarins such as furocoumarin have shown photoactivity potential. Exposure to both furacoumarins and UV in humans results in the development of burnt skin, also called phytophotodermatitis (Lagey et al. 1995). Studies by Kiviranta and Abdel-Hameed (1994) have developed and used *Artemia salina* (brine shrimp) for evaluating phototoxicity bioassays. In the same manner, psoriasis is a skin problem affecting the health and normal daily lives of a significant number of human beings (Disepio et al. 1999). The external appearance of skin may differ from one patient to another due to differences in epidermal keratinocyte hyperproliferation and strange keratinocyte demarcation. Medical specialists should handle psoriasis therapy with care in relation to diagnosis and treatment as varying responses and adverse effects may occur (Ashcroft et al. 2000). In 1948, el Mofty utilized xanthotoxin (*Ammi majus*) for the treatment of vitiligo, while Parrish and co-workers demonstrated in 1974 that two dermatologists (A. Lerner and T. Fitzpatrick) elaborated a more accurate remedy for the management of psoriasis. A combined treatment of xanthotoxin through oral administration and UV radiation (320-400 nm) has also proved effective as a means of psoriasis therapy (McNeely and Goa 1998).

Coumarins do not provoke phototoxic reactions, with a spectrum extending from 360-300 nm for diagonising contact photodermatitis in a concentration dependent manner (Kaidbey and Kligman 1981). *Artemia salina* (brine shrimp) is a bioassay test marine organism that is rapid and non-invasive for preliminary biological screening of large numbers of samples for phototoxicity. Athamantin and umbelliferone did not document any phototoxicity but linear furanocoumarins reported phototoxic activity in the following order: psoralen > bergapten > peucedanin > xanthotoxin (Ojala et al. 1999). Nigg et al. (1993) found that Persian limes were more phototoxic than Key limes due to the presence of different types of coumarin in the order: isopimpinellin > limettin > bergapten > xanthotoxin > psoralen. They also revealed that coumarins were 13 to 182 times less concentrated in lime pulp than in peels. Gallium corrole-coumarin dyads (2-Ga) has demonstrated photodynamic anti-tumor activity via apoptosis and S-phase arrest in SiHa cells (Cheng et al. 2018). Cheng et al. (2018) also reported photodynamic therapy of cancer with synthesized fluorinated coumarin substituted zinc (II) /silicon (IV) phthalocyanines.

Antihypertensive Activity

Vasodilatory effects of coumarin were reported in cultured myocardial cells (Namba et al. 1988). Visnadine (extracted from fruit of *Ammi visnaga*) exhibited peripheral and coronary vasodilator activities in treating angina pectoris (Iranshahi et al. 2009). Tchamadeu et al. (2010) discovered that *Mammea Africana* (methanol and dichloromethane extract) had antihyperglycemic properties and phytotoxic potential exhibited through metabolic changes in diabetic rats.

Antitubercular Activity

Umbelliferone, phellodenol A, psoralen, scopoletin, bergapten, (+)-(*S*)-marmesin, (+)-(*S*)-rutaretin and xanthyletin were documented in *Fatoua pilosa* whole plants. Scopoletin and umbelliferone showed phytotoxicity against *Mycobacterium tuberculosis* H37Rv with MIC values of 42 and 58.3 µg/mL, respectively (Chiang et al. 2010).

Table 4 Anti-inflammatory activities of the coumarin compounds/derivatives with concentration and inhibition rate

Compound	Concentration	Inhibition	References
Columbianetin, Libonoridin			Kang et al. 2009
Scopoletin			Pan et al. (2010)
Praeruptorin, Visnadin			Menghini et al. 2010
Fraxetin, Daphnetin			Pozharitskaya et al. 2010
Fukanemerin			Nazari and Ironshahi 2011
			Bahadır et al. 2011
			(2011
	100 μM	3.9	//
Athamantin	61 μM	50	//
	87 μM	50	//
Bergapten	10 mg/kg	39	Chen et al. 1995
	10 mg/kg	27	//
	100 μM	15.9	Roos et al. 1997
			//
	50 μM	6.3	Roos et al. 1997
Coumarin	20 mg/kg	34	Lino et al. 1997
	20 mg/kg	44	Leal et al. 2000
Umbelliferone	20 mg/kg	22	Lino et al. 1997
	20 mg/kg	5.8	Leal et al. 2000
	4100 μM	50	Okada et al. 1995
	3400 μM	50	//
	3400 μM	50	//
Herniarin	100 μM	65	Silvan et al. 1996
	100 μM	2.9	//
		50	//
Ledebouviellol	121 μM	50	//
	134 μM	33	//
Psoralen	100 μM	34	//
	100 μM	41.8	//
	0.5 μM	50	Garcia-Argaez et al. 2000
Scopoletin	231 μM	50	//
	10 μg	50	Farah and Samuelsson 1992
	2600 μM	50	Okada et al. 1995
	500 μM	50	//
	1000 μM	50	//
	100 μM	77	Silvan et al. 1996
	100 μM	8.8	//
Umbelliferone	10 mg/kg	44	Chen et al. 1995
	10 mg/kg	30	//
	20 mg/kg	38	Lino et al. 1997
	3100 μM	50	Okada et al. 1995
	2500 μM	50	//
	1900 μM	50	//
Xanthotoxin	100 μM	31	//
	100 μM	33	//
	10 mg/kg	40	Chen et al. 1995
	10 mg/kg	25	//
	100 μM	5	Roos et al. 1997
	100 μM	3.5	//
Thiazoline and thiazolidinone moieties	0.31 to 0.78 μM	Human cyclooxygenase (COX)-1 and COX-2 isoforms	Dawood et al. 2015
8-methylbenzo[h]coumarins, muralatins A & B	6 - 14.5 μM		Lv et al. 2014.
Esculetin, daphnetin, fraxetin			Hoult and Paya 1996
Marmin; Sphondin			Ling et al. (2002)
Umbelliferone-6-carboxylic acid			Zhao et al. (2012)
Ninhvanin, 8-geranyl-7-hydroxycoumarin, 6-(60,70-dihydroxy-30,70-dimethylocta-20-enyl)-7-hydroxycoumarin, 6-(7-hydroperoxy-3,7- dimethylocta-2,5-dienyl)-7-hydroxycoumarin, 6-(2-hydroxyethyl)-2,2-dimethyl-2H-1-benzopyran, luvangetin.	9.4 to 52.8μM	9.8 to 46.8	Anh et al. 2017

Table 5 Pharmacological and biological activities of Coumarin

Activity	References
Anti-Alzheimer's, anti-depression,	Goedert and Spillantini (2006); Anand et al. (2012); Patil et al. (2013, 2013); Greig et al. (2005)
	Anand et al. 2012; Sarker and Nahar 2017; Kirsch et al. 2016; Bubols et al. 2013; Al-Majedy et al. 2016; Patil et al. 2013, b; Najmanova et al. 2015; Terry and Buccafusco 2003; Joubert et al. 2017; Xie et al. 2015, 2016; Lan et al. 2017; Pisani et al. 2016; Xie et al. 2013; Piazzi et al. 2008; Domínguez et al. 2016; Weinreb et al. 2009; Hamulakova et al. 2016; Hashimoto et al. 2003; Soler-López et al. 2012; Munoz-Torrero 2008; Wolfe 2001; Faghih et al. 2015; Fernández-Bachiller et al. 2012; Thiratmatrakul et al. 2014; Hui et al. 2014; Minarini et al. 2013; Salomone et al. 2012; Hampel et al. 2010; Galimberti et al. 2013; Jack et al. 2010; Scheltens and Feldman (2003); Anand et al. 2012; Xie et al. 2013; Huang et al. 2015; Youdim and Bakhle (2006); Zatta et al. 2009; Piazzi et al. 2008; Jin et al. 2013; Zhou et al. 2008; Giacobini (2003); Castro and Martinez (2001); Weinstock (1999); Hoerr and Noeldner (2002); Kamal et al. 2008; Shaik et al. 2016; Meng et al. 2012; Tasso et al. 2011; Carreiras and Marco (2004); Viña et al. 2012; Ali et al. 2016a, b; Xie et al. 2015; Joubert et al. 2017;

Furthermore, phellodenol A, (+)-(*S*)-marmesin and xanthyletin also exhibited activity against tuberculosis (Cohen 1979).

Antibacterial and Antifungal Activities

As a SM, coumarin itself has demonstrated low antibacterial potential. However, it has been observed that derivatives of coumarin (with hydrocarbon substitution: ammoresinol and andostruthin) demonstrated strong potential against Gram-positive bacteria (e.g. *Micrococcus luteus*, *Micrococcus lysodeikticus*, *Staphylococcus aureus, Bacillus megaterium*) (Hodak et al. 1967). Raja et al. (2011) documented that furanocoumarin (imperatorin) extracted from *Angelica dahurica* and *Angelica archangelica* clearly showed phytotoxicity against *Shigella dysenteriae.* Prats et al. (2007) studied the phytotoxic impact of different coumarin compounds (scopolin, scopoletin and ayapin) on the head rot of sunflower. They demonstrated that scopolin showed more cytotoxic activity against *Sclerotinia* than the rest of the tested molecules. Basile et al. (2009) found that Gram-positive (*Corinebacterium diphtheria*, *Staphylococcus aureus*, *Streptomyces pneumoniae*, and *Streptomyces pyogenes*) and Gram-negative bacteria (*Pasteurella, Neisseria meningitides* and *Haemophillus influenza*) growth was significantly inhibited by phytotoxins "novobiocin" from fungi (*Streptomyces niveus* and *Streptomyces spheroides*). Gellert et al. (1976) studied the phytotoxic behavior of coumaermycin and found that it significantly retarded DNA supercoiling as catalyzed by *Escherichia coli*, being 50% more potent than novobiocin.

Many coumarin derivatives have showed strong antibacterial, anticoagulant and antifungal properties (Fig. 2; Zhang et al. 2016). Zavrsnik et al. (2011) found that some 3-cynnamoyl- -4-hydroxycoumarins possess good antibacterial activity (inhibition zones against *Staphyloccocus aureus* ranged between 16 to 27 mm). Montagner et al. (2008) demonstrated the antifungal properties of coumarin derivatives with metal complexes against *Microsporum canis, Fusarium solani, Candida glaberata*, *Trichophyton longifusus, Candida albicans* and *Aspergillus flavus.* Rehman et al. (2005) documented phytotoxicity against several bacterial strains like *Corynebacterium diphtheriae, Staphylococcus aureus*, *Streptococcus pyogenes, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Salmonella typhi, Shigella dysenteriae* and *Bacillus cereus*. Moreover, metal complexes possess more antibacterial and antifungal properties and are potential candidate compounds for developing novel antifungal agents.

Antiviral and anti-HIV activities

A series of SMs possessing the coumarin nucleus have shown antiviral properties against different microbes. Certain coumarin derivatives have shown to be active against viruses (Fig. 3). Coumarins were also studies in human immunodeficiency virus (HIV) research. Iranshahi et al. (2008) isolated two furanocoumarin esters (fesumtuorin A, B, one bicoumarin, fesumtuorin C, five spirobicoumarins, fesumtuorin D, E, F, G and H) from the dried root extract of *Ferula sumbul*, reporting the anti-HIV properties of these coumarins compounds.

The antiviral and antitumour potential of coumarin–benzimidazole hybrids have already been documented (Paul et al. 2013; Tsay et al. 2013). The coumarin derivative dicamphanoyl khellactone or DCK has shown significant toxicity against HIV-1 replication (Mehrdad et al. 2010). Chen et al. (2000) also reported that some coumarin derivatives (hystrolinone, quinolinone, hystroxene-I and (+)-hopeyhopin) isolated from *Citrus hystrix* roots present antibacterial and anti-HIV properties. Jo et al. (2002) isolated some coumarins (Inophyllum A, inophyllum B, inophyllum C, inophyllum E, inophyllum P, inophyllum G1 and inophyllum G2), from giant African snails (*Achatina fulica*). They found that inophyllum B and P inhibited HIV reverse transcriptase (RT) with IC_{50} values of 38 and 130 nM. The stem bark of *Chlophyllum brasiliense* possessed GUT-70 that showed significant toxicity and inhibition against HIV-1 cells, with the mechanism of suppression through NF-κB (Chen et al. 1995). This SM

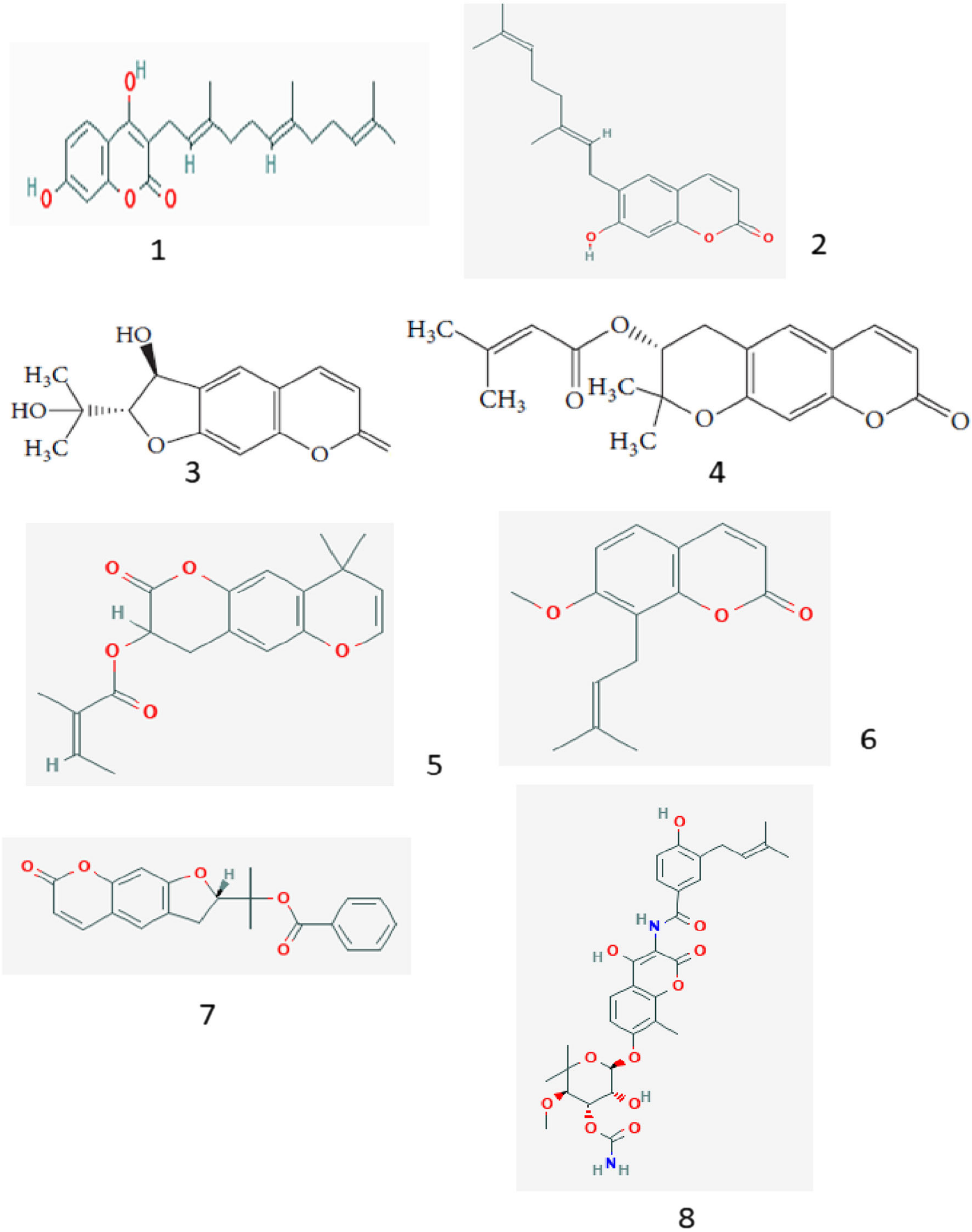
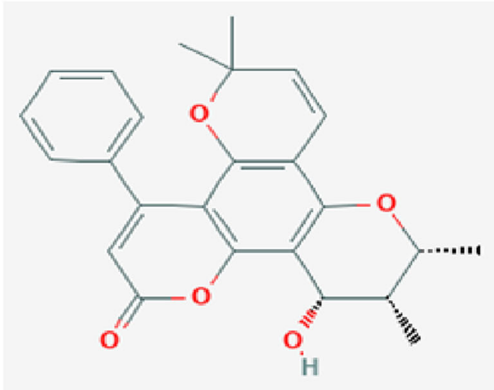


Fig. 2 List of some coumarins/derivatives used as antibacterial agents. 1: Ammoresinol; 2: ostruthin; 3: anthogenol; 4: Grandivittin; 5: agasyllin; 6: osthole; 7:Felamidin; 8: Novobiocin

was a lead compound for the preparation of therapeutic agents against HIV-1 disease. Four new coumarin glycosides, 7-O-(3-O-sinapoyl-β-D-glucopyranosyl)-6-methoxycoumarins, 7-O-(6-O-sinapoyl-β-D-glucopyranosyl)-6-methoxycoumarins, 7-O-(2-O-sinapoyl-β-D-glucopyranosyl)-6- methoxycoumarins and 7-O-(6-O-syringoyl-β-D-glucopyranosyl)-6-methoxycoumarins, together with eight previously described coumarin derivatives isolated from the roots and stems of *Erycibe obtusifolia* were shown to be active agianst respiratory syncytial virus. In the same manner, a few coumarin derivatives also showed greater potency against influenza A virus (H1N1) (Lee et al. 2011).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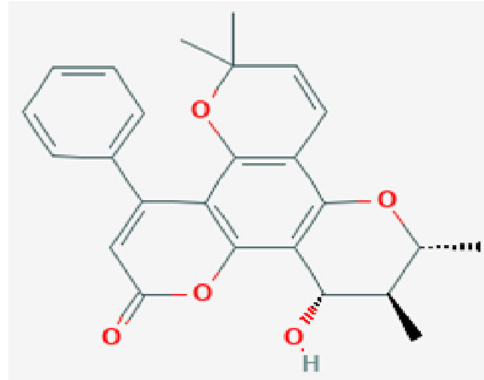
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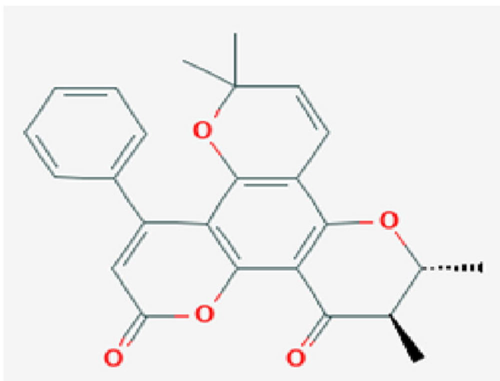
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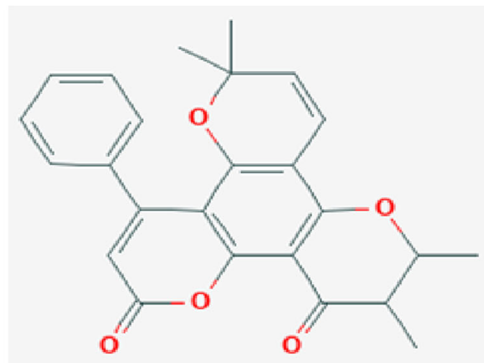
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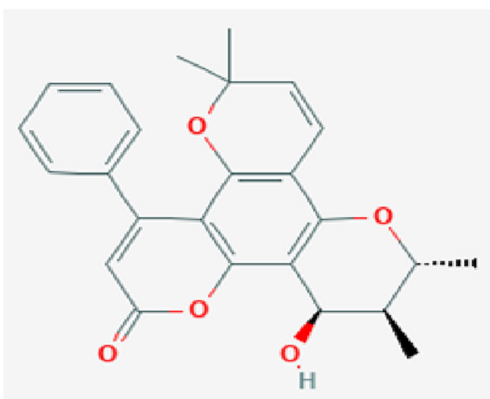
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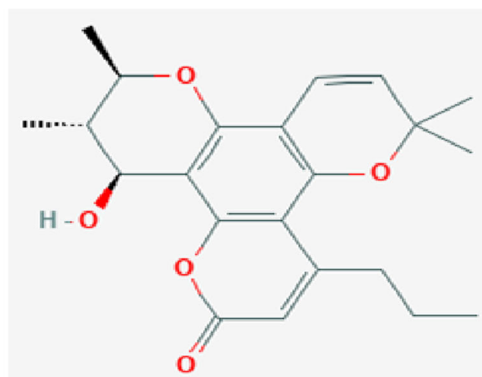
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Fig. 3 List of some coumarins/derivatives used as antiviral/anti-HIV agents. 1: Inophyllum A; 2: inophyllum B; 3: inophyllum C; 4: inophyllum E; 5: inophyllum P; 6: (+)-calanolide A

Two isomers, (+)-calanolide and (−)-calanolide, were identified in the leaves of *Calophyllum lanigerum* and reported to possess phytotoxicity against HIV-1 infection (Li et al. 2013). Moreover, Tsai et al. (2000) found that (+)-calanolide A demonstrated inhibition of HIV-1 while other coumarin derivatives (−)-dihydrocalanolide B and (−)-calanolide B also demonstrated the same antiviral activity. Chang et al. (1997) separated calanolide F and pseudocordatolide C from *Calophyllum lanigerum* var. austrocoriaceum and *Calophyllum teysmannii* var. inophylloide (King) P. F. Stevens and demonstrated that both compounds and their latex possess anti-HIV activity.

Antitumor and Anti-Cancer Activities

Biological investigation of coumarins and their derivatives has revealed a promising therapeutic role in a number of cancer types depending on their location in the body. Various pathways are involved in different cancer types, where a majority of studies are conducted in the breast, pancreatic cells, skin, prostate and brain amongst others. The coumarin derivative osthole was effective in reducing migration of breast cancer as well as inhibiting the metalloproteinase promoter and enzyme function (Xihong et al. 2006). Furthermore, two ER+ human breast cancer cell lines demonstrated significantly inhibited proliferation under coumarin (neo-tanshinlactone) treatment, with the effect being 10-fold more potent than tamoxifen (Xihong et al. 2006). In MCF-7 (human breast adenocarcinoma cell lines), different coumarin compounds substituted by benzothiole have shown specific inhibition activities (Kini et al. 2012). Sashindhara et al. (2012) developed a hybrid molecular approach, where a coumarin-monastrol hybrid utilized by combining two bioactive pharmacophore coumarin-monastrols as anticancer agents. These hybrids showed impressive activity against the MCF-7 and MDB-MB-231 cell lines. To evaluate the mechanisms underlying the anticancer activity of this hybrid, apoptotic studies, caspase-3 activation assay and cell cycle analysis were performed. These studies revealed that apoptosis was induced by caspase-3 activation in both primary and metastatic breast cancer cells irrespective of ER status (Sashidhara et al. 2013).

Utilizing docking assays and e-pharmacophore, Manidhar et al. (2012) reported that human NAD (P) H:quinone oxidoreductase-1 and human phosphodiesterase 4B enzymes showed significant anticancer activity in pancreatic cancer while the same compounds also demonstrated antitumor activity against skin cancer in mice (Manidhar et al. 2012). Nasr et al. (2014) evaluated coumarin derivatives for anticancer activity in resistant pancreatic cells and drug sensitive cell lines, where coumarin compounds were effective than the reference drug. Fujioka et al. (1999) studied the phytotoxicity of various coumarin derivatives and found that copoletin, japoangelone, and oxypeucedanin methanolate were highly active in B16F10 (melanoma cells) cells than MK-1 and HeLa cells, whereas xanthotoxin and bergapten were more active in HeLa compared to MK-1 cells following a change in position 8 of 4-methyl-7-hydroxycoumarins.

Esculetin (6, 7-dihydroxycoumarins), a coumarin which has antitumerogenic properties, can be extracted from *Artemisia capillaries*, *Citrus limonia* and *Euphorbia lathyris*. Kok et al. (2009) found enhanced apoptosis induced by Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) in SAS (oral cancer) cells lines by esculetin (Lee et al. 2011). The antitumerogenic activity in primary brain cultures showed that it rescued *N*-methyl-D-aspartate-dependent toxicity (Rosselli et al. 2009)· Furthermore, coumarins such as grandivittin, agasyllin, aegelinol benzoate and osthole from *Ferulago campestris* showed low cytotoxicity in the A549 lung cancer cell line (Portugal et al. 2001). Psoralidin, an angular type furanocoumarin can be isolated from the seeds of *Psoralea corylifolia* (Zhao et al. 2005; Xiao et al. 2010) and is toxic against the SNU-1, SNU-16 (gastric cancer), HT-29 (colon cancer) and MCF-7 (breast cancer) cell lines. Psoralidin can also induce apoptosis in both androgen-dependent (LNCaP, C4-2B) and androgen-independent (DU-145, PC-3) prostate cancer cells, as well as slow growth of PC-3 xenograft tumors in mice (Yang et al. 1996; Mar et al. 2001; Pahari and Rohr 2009; Kumar et al. 2010; Srinivasan et al. 2010).

Myers et al. (1994) found coumarins to inhibit proliferation of two renal carcinoma cell lines (786-O and A-498) and two malignant prostatic cell lines (DU145 and LNCaP) following 5 days of treatment. Among these, the LNCaP cell line was most sensitive to the coumarins. Wu et al. (2003a, b) found pyranocoumarin-induced apoptotic cell death in drug sensitive KB-3-1 and multidrug resistant KB-V1 cancer cell lines. According to some studies, Pyranocoumarins synergize the effects of other antitumor drugs such as vincristine, doxorubicin and paclitaxel. Mousa (2002) found the anticoagulative effects of unfractionated heparin and warfarin (coumarins) to prevent tumor formation by restricting tumor cells to the pulmonary microvasculature. Isoflovin is a protective agent against breast cancer. The coumarins melilunumarin A, 6-deoxyhaplopinol and marmesin exhibited significant inhibition of early antigen activation in Epstein-Barr virus induced by 12-O-tetradecanoylphorbol 13-acetate in Raji cells, demonstrating cancer chemopreventive activity (Ito et al. 2017).

In recent years, newly designed hybrid molecules with multiple pharmacophores showed interesting biological profiles. The same technology used for cancer therapy, demonstrated that a single molecule have mutiple pharmacophores and different modes of action that may be more beneficial (Mayur et al. 2009; Solomon et al. 2009). Furthermore, Belluti et al. (2010) reported the anticancer activities of a hybrid stilbene and coumarin compound. Coumarins could exert anticancer activity via a variety of mechanisms, including inhibiting the telomerase enzyme (Wu et al. 2014), inhibiting protein kinase activity and down-regulating oncogene expression. Bronikowska et al. (2012) found another furanocoumarin (psoralidin) isolated from *Psoralea corylifolia* with anticancer properties. TRAIL elicits apoptosis in cancer cells with lesser or no cytotoxicity towards normal tissues, with endogenous TRAIL being critical to the immune response. TRAIL-induced apoptosis through modulated by coumarins in cancer cells and psoralidin augments the anticancer effects of TRAIL. Additionally, researchers have shown that coumarins were able to suppress proliferation of cancer cells by arresting the cell cycle in the G0/G1 (Wu et al. 2014) and G2/M phases (Chen et al. 2012), as well as by affecting the p-gp of cancer cells (Fong et al. 2008; Zhou et al. 2010). Hydroxycoumarins exert anticancer activity by generating free radical species in cancer cells producing oxidative stress, leading to pro-apoptic effects (Zhou et al. 2010). Huang et al. (2011) reported that coumarins inhibited protein kinase 2 (PK2) and abolished proliferation of cancer cells.

The cytotoxicity of several coumarins extracted from *Ferula pseudalliacea* roots was evaluated in the HeLa human cancer cell line. However, among the tested compounds, only sanandajin, farnesiferol B, and kamolonol acetate coumarins displayed the highest potency against HeLa cells with IC50 values of 2.2, 6.7, and 4.9 μM, respectively (Dastan et al. 2014). The pattern of substitution on the basic coumarin core structure influences pharmacological as well as biochemical properties, including therapeutic applications (Kofinas et al. 1998; Musa et al. 2010; Carotti et al. 2002). The anticancer activities of various coumarins have also been extensively studied in A549 (lung), ACHN (renal), H727 (lung), MCF-7 (breast) and HL-60 (leukemia) cancer cell lines, with antiproliferative properties being evident in all cases. Moreover, the anticancer and antiapoptotic activites of coumarins have confirmed in clinical trials of prostate cancer, malignant melanoma and metastatic renal cell carcinoma (Iranshahi et al. 2009; Bruneton 1995; Egan et al. 1990a, b; Harborne 1999; Walker et al. 2003; Pastirova et al. 2004).

Coumarins as a therapeutic agent for Alzheimer and Parkinson's diseases

Alzheimer's disease (AD) is a kind of neurodegenerative disorder, deposits of improper proteins namely β-amyloid (Aβ) and neurofibrillary tangles, and characterized by progressive memory loss and impedance in language skills and brain degenerative behaviour (Goedert and Spillantini 2006). Meanwhile, accumulation of reactive oxygen species, free radical production, inflammation, calcium dysregulation and neuronal cell membrane damage leading to neuronal dysfunction.

Scientists have documented that several factors are responsible for this brain disorder and impairment such as cholinergic dysfunction, t-protein aggregation (Grundke-Iqbal et al. 1986), amyloid-b (Ab) deposits (Castro and Martinez), and oxidative stress (Gella and Durany 2009; Coyle and Puttfarcken 1993) are considered. According to Talesa (2001), in AD, there are severe loss of cholinergic neurons that exhibit the deficiency of acetylcholine (ACh) in specific regions of the brain that mediate learning and normal functions of memory. Therefore, patients suffered from AD and treated with medication had shown an inhibition of acetylcholinesterase (AChE) but have very low therapeutic success due to the disease complexicity. Researchers were able to find another compound that inhibits the butyrylcholinesterase (BuChE) (Greig et al. 2005). Any compound that show phytotoxic potential and inhibit both AChE and BuChE has value that is more therapeutic in the treatment of AD.

A disturbance in the neurotransmitter systems (dopaminergic and serotoninergic) might be responsible for change in mood and behaviour observed in AD (Dringenberg 2000). This support the fact that inhibitors of monoamine oxidase could be helpful in AD treatment. The various therapeutic approaches for AD management have directed to decrease its production or aggregation, or increase its removal. A compound that exhibits the dual binding properties with AChE represents new chemistry for therapeutic treatment of AD. Researchers have demonstrated that naturally occurring and chemically synthesized coumarin derivatives had potent phytotoxicity to inhibit AChE inhibitory activity (Changwong et al. 2011).

Coumarin and coumarin derivatives has shown inhibition of oxidative stress and freed radicals generation and protect the neurons (Kontogiorgis et al. 2007). In mice, a plant based natural coumarin have proved intracerebroventricular injection of A□-induced memory impairment (Yan et al. 2004). The coumarins primarily interact with PAS of AChE21 and accordingly, most of the scientists have put their efforts in synthesizing dual inhibitors of AChE by incorporating a catalytic site interacting moiety with coumarin through an appropriate spacer. Initial reports have demonstrated that coumarin derivatives were able to counteract and inhibit the AChE through binding to PAS (Radić et al. 1984). Recently ensaculin 1 (KA-672 HCl), a coumarin derivative has shown potent therapeutic effect including AChE inhibition (Hilgert et al. 1999). Different coumarin derivatives have been synthesized that showed significant inhibition against AChE with additional therapeutic potential that are important for the treatment of AD (Piazzi et al. 2003).

Conclusions

Among SMs, coumarins are natural phytochemicals that have evolved as an integral part of the diverse interactions between plants and their abiotic environment. The purpose of this review is to increase awareness of the biological and pharmacological multifunctionality of coumarins and related derivatives. Ecologists, biochemists and molecular biologists should join hands and efforts for further exploration in understanding coumarin functionality. Coumarin compounds may be beneficial for plants as natural antipathogenic compounds, and for human beings as pharmaceutical supplements based on their anticancer, antimicrobial, anti-Alzheimer and anti-Parkinson's diseases and anti-inflammatory effects, as well as reference compounds in various bioactivity tests. However, further study on the mode of action and therapeutic potential of coumarins in cancer and other diseases are necessary to divulge the involved molecular mechanisms.

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Compliance with ethical standards

Confict of interest The authors declare no competing financial interests.

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