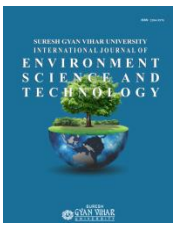

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Review article

Sources and biological activity of Coumarins: An Appraisal

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Keywords

Natural coumarin Source biological activities

Abstract

Coumarin was first isolated as a natural product in 1820 and named as derived from the French word for the seeds of Tonka bean, *coumarou*, *Dipteryx odorata* (*Coumarouna odorata*) (*Leguminosae/ Fabaceae*). The structure of heterocyclic compound is found in most of the drugs that is the reason why heterocycles are of vital interest in the pharmaceutical and agrochemical science. In the metabolism of most of the living cells various heterocyclic compounds plays important role. In addition, a wide variety of pharmacological, biological and physiological activities are also exhibited by O-based heterocyclic aromatic coumarin compounds. There are following pharmacological activities for example; anti-cancerous, anti-coagulant, anti-oxidant, anti-HIV, anti-inflammatory and anti-bacterial which are exhibited by coumarin. Various sources of natural coumarins and their biological activities are compiled in the present review article.

Introduction

Heterocyclic compounds have an important part in the pharmaceutical industry for the search of effective bioactive agents. More than 90% of pharmaceutical drugs have a heterocyclic ring, e.g. penicillin, quinoline, which contains heterocyclic structures are used as analgesics, antibiotics and anti-tumor drugs. Many of the heterocyclic compounds were isolated from natural resources and various synthetic methods were also developed for their synthesis. Major sources of complex heterocyclic compounds are the microorganisms which are used as antibiotics in various infectious diseases. The coumarins are classify under

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the benzopyrone family of heterocyclic compounds in which 6-membered α-ring and generally occurs in various natural products as a benzo derivative.

Coumarin and its derivative compounds represent one of the most active class that exhibit various types of biological activity such as antibacterial (Al-Amiery et al. 2014; 2016; 2016), antifungal (Al-Amiery et al. 2012), anti-inflammatory (Al-Amiery et al. 2013), anticoagulant (Al-Amiery et al. 2011), anti-HIV (Al-Ayed 2011) and antitumor agents (Al-Azawi et al. 2016). Coumarins are extensively employed as additives in cosmetics, food and perfumes (Al-Majedy et al. 2016) and as pharmaceuticals and optical brighteners (Al-Majedy et al. 2014) and would disperse in fluorescent and laser dyes (Al-Majedy et al. 2016).

Sources of Coumarins

Coumarins are found in significant quantities in plants, and its presence in microorganisms and animal sources has also been detected. Coumarin is naturally present in many plants, especially in high amounts in the tonka bean (*Dipteryx odorata*), vanilla grass (*Anthoxanthum odoratum*), sweet woodruff (*Galium odoratum*), mullein (*Verbascum* spp.), pyrone ring fused with benzene

sweet grass (*Hierochloe odorata*), cassia cinnamon (*Cinnamomum cassia*), sweet-clover (*Melilotus* sp.), deer tongue (*Dichanthelium clandestinum*), and the leaves of many cherry blossom tree (*Prunus* genus). *Cinnamomum zeylanicum* the true cinnamon (Ceylon cinnamon) contains little amount of coumarin (Leal 2000; Lino 1997).

The important dietary sources of coumarins are species of *Apiaceae* and *Rutaceae* family. Besides fruits and vegetables some essential oils and beverages are also the sources of coumarins. These essential oils are used as flavoring agents in foods. **Table 1** is showing certain literature reports on dietary sources of coumarins. Aroma of coumarin was sweet, aromatic, creamy vanilla bean odour with nutlike natures. In human diet the main source of coumarin is cinnamon which is considered as a spice and comes from the dried bark of *C. cassia/C. aromaticum* and *Cinnamomum verum.* In preparation of desserts, cakes, candy, etc. and in many curries and other dishes Cinnamon is widely used as flavoring agents.

Table 1: Dietary sources of coumarins

S. No.	Family	Food source	Reference
1	Apiaceae	Aniseed, carrots, celery, coriander, cumin, fennel and parsley	(Jaw-Ming et al. 2008)
2	Rutaceae	Citrus and some other fruits such as Bael	(Trease and Evans 2009)
3	Lauraceae	Chinese cinnamon oil, cinnamon bark oil	(Choi et al. 2001)
4	Lamiaceae	lavender oil	(Bourgaud et al. 2006)

5	Oleaceae	olive oil	(Rosselli et al. 2009)
6	Ericaceae (Heath family)	Bilberry	(Nykanen 1984)
7	Rosaceae (Rose family)	Cloudberry	(Nykanen 1984)
8	Theaceae	Black and green tea	(Sonnenberg et al.1995)
9	Rubiaceae.	coffee	(Sonnenberg et al.1995)
10	Others	Wine	(Sonnenberg et al.1995)

TDI (Tolerable daily intake) of coumarin derivatives are 0.1 mg/kg (Lake 1999) and the maximum permissible level for food and beverages is 2 mg/kg (European Council 1988). Estimated value of coumarins diet is about 0.02 mg/kg/day and estimation of TAMDI (Theoretical added maximum daily intake) of coumarin through food is 4.085 mg/day (0.07 mg/kg/day) (AFC 2004).

Many medicinal compounds has been discovered and researchers are trying to improve the therapeutic activity and reduced the toxicity by modify the chemical structure of active part of the drugs. Coumarin is a natural product isolated from plant and it showed various biological activities.

Due to odour strength, tenacity, stability to alkali and relatively cheap price synthetic coumarins are used as a sweetener and fixative in perfume, fragrance enhancers for natural essential oils, blenders in soaps and detergents, aroma enhancers in tobacco and for imparting pleasant odours to industrial products.

According to chemical structure natural coumarins are classified in to six groups-

1. Simple coumarins that are compounds which formed coumarin derivatives by the reactions; hydroxylation, alkoxylation and alkylation on the benzene ring of coumarin. Ammoresinol, Chartreusin, Coumermysin, Novobiocin and Ostruthin are related to simple coumarins with antibacterial activity and Osthole exhibits anticancer activity (Venugopala 2013).
2. Furanocoumarins class consists of Bergapten, Imperatorin, Marmalde, Psoralen and other compounds that exhibit antifungal, anti-inflammatory and anti-TB activities.
3. Dihydrofurano coumarins consist of five-member furan ring which is attached to the benzene ring of coumarin.
4. Pyranocoumarins that have 6-membered pyran ring attached to a benzene ring of coumarin and it is further divided in to

two types linear and angular Pyranocoumarins. Linear type consist of Aegelinol benzoate, Agasyllin and Grandivittin (Basile et al. 2009) exhibited anti-bacterial activity and antiviral activity shown by angular type coumarins, Calanolide (A, B, F), Inophyllum (A, B, C, E, P, G) (Mishra et al. 2013) and Pseudocordatolide (Venugopala 2013).

5. Phenylcoumarins and 6. Bicoumarins in which substitution in pyrone ring which is generally at position C_3 or C_4 and have the pharmacological anticoagulant activity.

Isolation of Coumarins

Major coumarin constituents that have been isolated (from plants) are: simple furocoumarins and isofurocoumarins, hydroxycoumarins, biscoumarins, pyranocoumarins, and dihydroisocoumarins (Ribeiro and Kaplan 2002). Several plant species distributed over 40 different families are found which contains coumarins.

Coumarins have been obtained from many plants species distributed over the 40 different families. More than 1300 coumarins have been isolated, which were well distributed in families of *Angiospermae*, *Dicotyledoneae* and *Monocotyledoneae*. In all angiosperm, simple coumarins are the most common, most notably in *Asteraceae* and *Oleaceae*, and the furocoumarins and pyranocoumarins were second most prevalent coumarins (Ribeiro and Kaplan 2002).

Skalicka-Wozniak et al. (2018) isolated rare coumarins from fruits of Peucedanum luxurians. They reported that in most cases, with dichloromethane as solvent the fruits gives higher concentrations of most of the investigated coumarins as compared to the aerial parts, with peucedanin compound is identified that it present in great quantity of 4563.94 ± 3.35 mg/100 g concentration. Various gram-negative and gram-positive bacterial strains were used for testing the efficiency of isolated coumarin compounds.

Mustafa et al. (2018) used two methods which are serial soxhlet extraction and kinetic maceration using water, methanol, chloroform, and n-hexane as extraction solvents for the isolation of coumarins from Creston apple seeds. In vitro anti-cancerous (cytotoxic) activity of the mentioned coumarin derivatives was studied by using MTT assay on three cancer cell lines, AMN3, HeLa and MCF-7. The results indicated that against AMN3 and HeLa cell lines, all compounds have higher IC50 values as compared to 5-fluorouracil and against MCF-7 cell line, some compounds have IC50 values which was lower than 5- fluorouracil.

Phytochemicals and nutritional values of plants have been studied for decades and then added as important part of our daily diet. Gogoi (2017) isolated coumarins from *Mesua assamica* plant which is endemic to Assam in India and reported its cytotoxic (anti-cancerous) activity. *Mesua assamica* plant belongs to family Clusiaceace, is a slow growing tall evergreen tree. Isolation of various coumarin-derivatives from fruit peels, root and barks, and charactessrization have been done, which are further used as effective anti-cancer agents. Some natural coumarin novobiocin, coumermycin, and clorobiocin were isolated from microbial sources such as *Streptomyces* and *Aspergillus* species (Cooke 1998; Lacy and O'kennedy 2004; Yadagiri et al. 2014).

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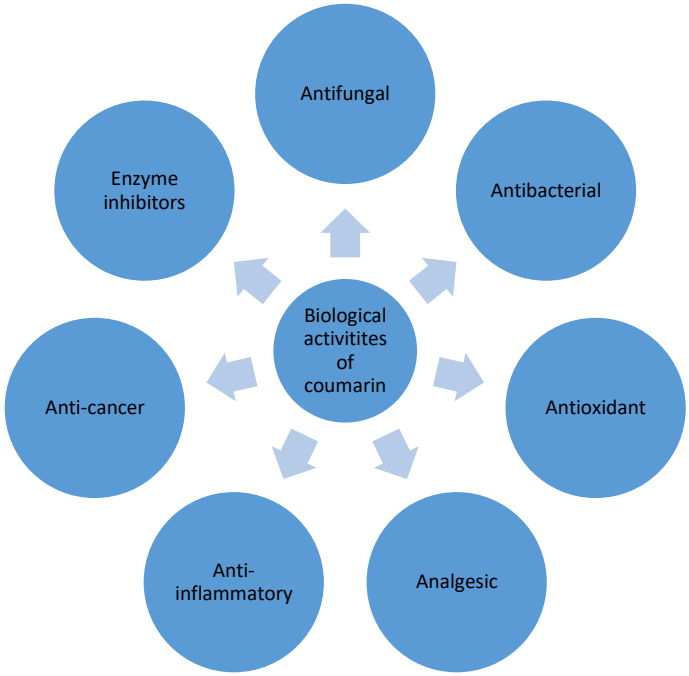
Biological Activity of Coumarins

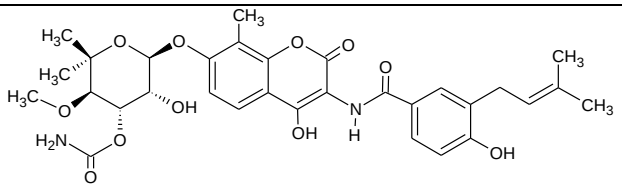
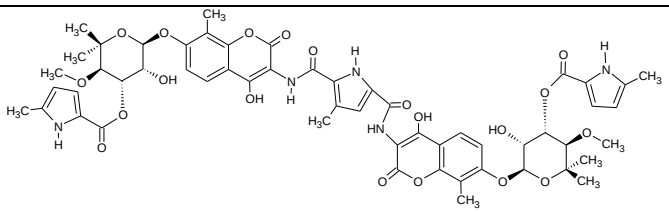
Coumarin and its derivatives are biologically and pharmacologically active compounds with a broad range of properties as antimicrobial, antitumor, anti-HIV, anti-inflammatory, anticoagulant and antioxidant agents. In this review article various biological activities of natural coumarins are highlighted.

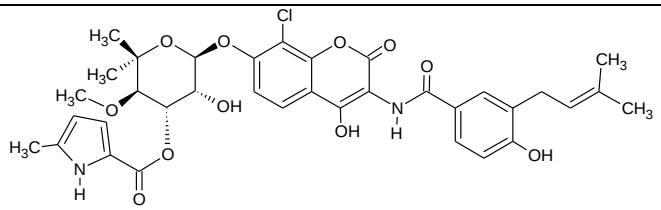
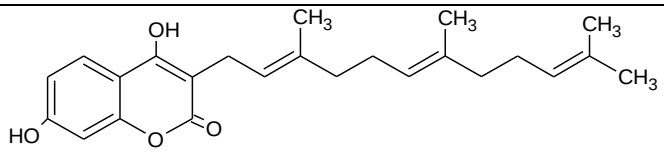
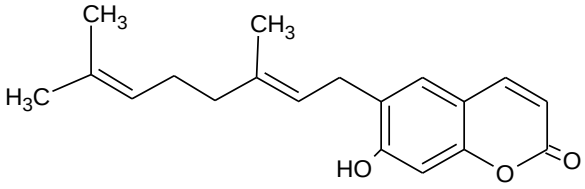
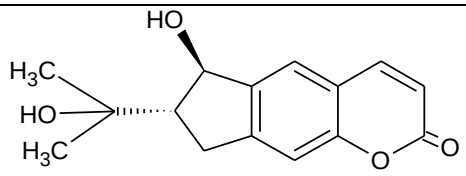
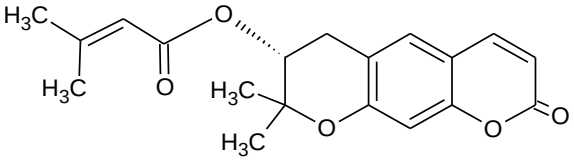
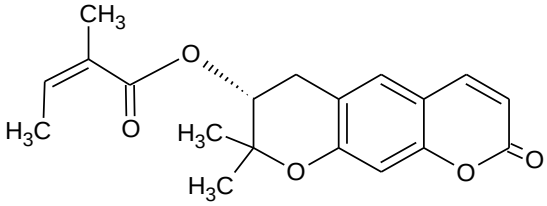


a. Antibacterial activity

For prevention or treatment of bacterial infections antibacterial or antibiotics were used and they act either by inhibiting the growth of bacteria or killing the bacteria (**Table 2**).

Table 2: Antibacterial activity of some natural coumarins

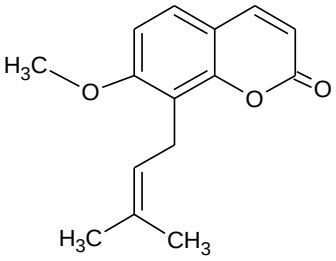
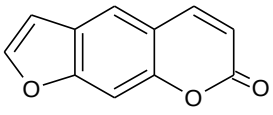
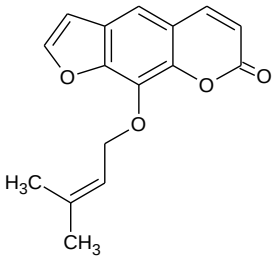
S. No.	Coumarins	Structure	Antibacterial activity against the species	Reference
1.	Novsobiocin (from *Streptomyces* and *Aspergillus* species)		-	(Cooke 1998)
2.	Coumermycin (from *Streptomyces* and *Aspergillus* species)		-	(Lacy and O'kennedy 2004)

3.	Clorobiocinz (from *Streptomyces* and *Aspergillus* species)		-	(Yadagiri et al. 2014)
4	Ammoresinol		*B. megaterium, M. luteus, M. lysodeikticus, S. aureus*	(Venugopala 2013)
5	Ostruthin		*B. megaterium, M. luteus, M. lysodeikticus, S. aureus* *Anti fungal activity*	(Venugopala 2013; Bourgaud et al. 2006)
6	Anthogenol (from green fruits of *Aegle marmelos*)		*Enterococcus* bacteria	(Evans 2009)
7	Agasyllin		Antibacterial activity *S. aureus, S. typhi, E cloacae,* and *E aerogenes*	(Razavi et al. 2013)
8	Aegelinol		Antibacterial activity *S. aureus, S. typhi, E cloacae,* and *E aerogenes*	(Adhami et al. 2013)

b. Antifungal activity

The fungal infection is generally found in hair, nails and skin. Ringworm and athlete's foot are some common fungal infections. Medications that are used to treat fungal infections are known as antifungal drugs. Certain coumarins, their structures and antifungal activities are compiled in **table 3.**

Table 3: Antifungal activity of some natural coumarins

S. No.	Coumarins	Structure	Antifungal activity against the species	Reference
1	Osthole		*B. cinerea*, *F. graminearum*, *P. capsici*, *R. solani* and *S. sclerotiorum*	. (Wang et al. 2009)
2	Psoralen		Antifungal activity	(Liu et al. 2005)
3	Imperatorin		Antifungal activity	(Wei et al. 2009; Parast et al. 2011)

c. Anti-coagulant and Cardiovascular

Coumarin derivatives possessed cardiovascular and anticoagulant properties. Warfarin (Fig. 1) is a synthetic coumarin analogue that is used as an anticoagulant and is known commercially with the trade name Coumadin.

Coumarins, as a kind of vitamin K antagonists (Schalekamp and de Boer 2010) the most remarkable are phenprocoumon, acenocumarol, and warfarin which are currently using in many countries (Daly 2013; Milatova and Milata 2013). Warfarin is used more oftenly than acenocoumarol due to its longer half-life (36 h), provides theoretically more stable anticoagulation and avoids fluctuations of factor VII that potentially lead to acenocoumarol treatment (half-life 10 h) (Beinema et al. 1998). The structure and anticoagulant activity of warfarin (a coumarins derivative) is also described in the literature (Schalekamp and de Boer 2010; Narayanaswamy et al. 2014).

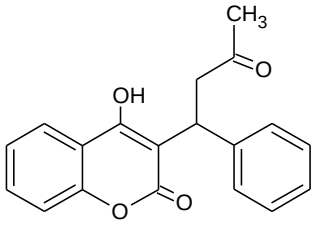
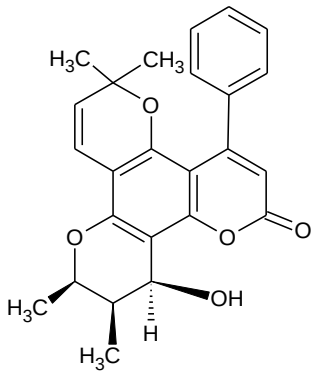
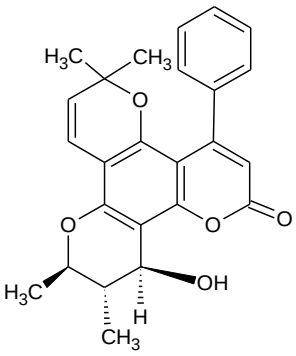
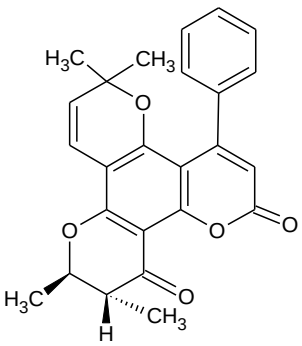


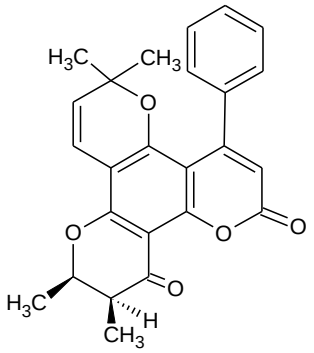
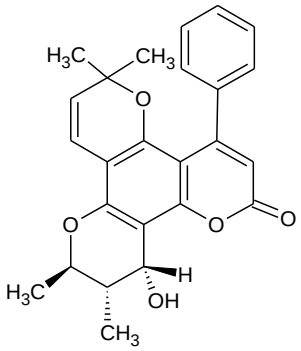
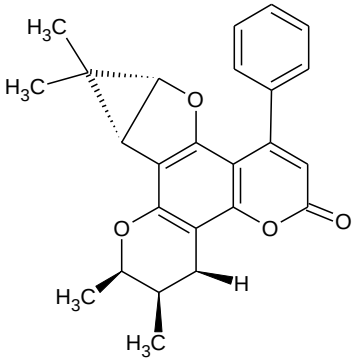
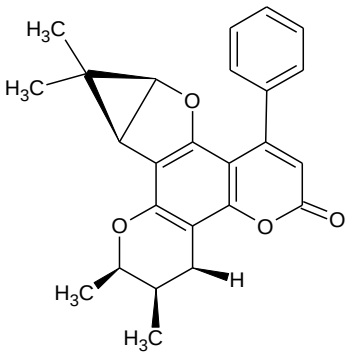
Fig. 1 Structure of Warfarin

d. Anti-Viral:

Coumarins showed the antiviral activity against HIV-1 protease (HIV-PR) and HIV-1 integrase. Literature reveals the anti HIV activity of coumarin derivatives, as shown in table 4 herein certain example of anti HIV agents, their structures and activity on certain species are also mentioned in this table.

Table 4: Anti-HIV activity of some natural coumarins

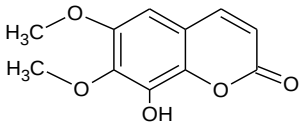
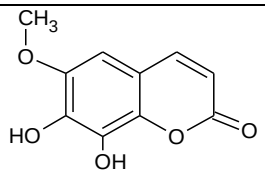
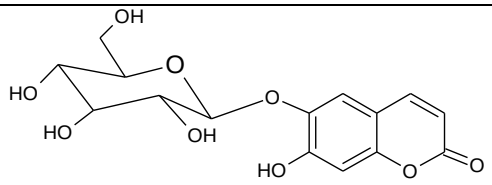
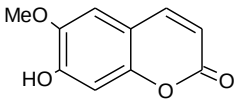
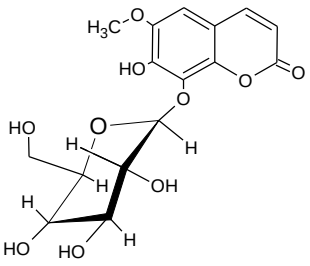
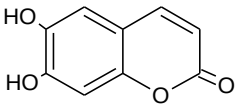
S. No.	Coumarins	Structure	Anti-HIV activity against the species	Reference
1	Inophyllum *A*		Giant African snail, *Achatina fulica*	(Prasad et al. 2012; Yimdjo et al. 2004; Patil et al. 1993; Ali et al.1999)
2	Inophyllum B		Giant African snail, *Achatina fulica*	(Prasad et al. 2012; Yimdjo et al. 2004; Patil et al. 1993; Ali et al. 1999)
3	Inophyllum C		Giant African snail, *Achatina fulica*	(Prasad et al. 2012; Yimdjo et al. 2004; Patil et al. 1993; Ali et al. 1999)

4	Inophyllum E		Giant African snail, *Achatina fulica*	(Prasad et al. 2012; Yimdjo et al. 2004; Patil et al. 1993; Ali et al. 1999)
5	Inophyllum P		Giant African snail, *Achatina fulica*	(Prasad et al. 2012; Yimdjo et al. 2004; Patil et al. 1993; Ali et al. 1999)
6	Inophyllum G1		Giant African snail, *Achatina fulica*	(Prasad et al. 2012; Yimdjo et al. 2004; Patil et al. 1993; Ali et al. 1999)
7	Inophyllum G2		Giant African snail, *Achatina fulica*	(Prasad et al. 2012; Yimdjo et al. 2004; Patil et al. 1993; Ali et al. 1999)

e. Antiadipogenic activity

Several natural compounds exhibit strong capacity for decreasing triglyceride accumulation, enhancing lipolysis and inducing apoptosis. The present review paper reported the sources of coumarins and their structure in **table 5**.

Table 5: Antiadipogenic activity of some natural coumarins

S. No.	Coumarins	Structure	Reference
1	Fraxidin (stem barks of *Fraxinus rhynchophylla* dence Oleaceae)		.(Zhu and Hou 2008; Michalska and Kisiel 2014; Hu et al. 2011; Oshima et al. 2013)
2	Fraxetin (stem barks of *Fraxinus rhynchophylla* dence Oleaceae)		.(Zhu and Hou 2008; Michalska and Kisiel 2014; Hu et al. 2011; Oshima et al. 2013)
3	Esculin (stem barks of *Fraxinus rhynchophylla* dence Oleaceae)		.(Zhu and Hou 2008; Michalska and Kisiel 2014; Hu et al. 2011; Oshima et al. 2013)
4	Scopoletin (stem barks of *Fraxinus rhynchophylla* dence Oleaceae)		.(Zhu and Hou 2008; Michalska and Kisiel 2014; Hu et al. 2011; Oshima et al. 2013)
5	Fraxin (stem barks of *Fraxinus rhynchophylla* dence Oleaceae)		.(Zhu and Hou 2008; Michalska and Kisiel 2014; Hu et al. 2011; Oshima et al. 2013)
6	Esculetin (stem barks of *Fraxinus rhynchophylla* dence Oleaceae)		.(Zhu and Hou 2008; Michalska and Kisiel 2014; Hu et al. 2011; Oshima et al. 2013)

f. Anticancer

It is a worldwide serious human health disease and in United States cancer is the second leading disease which causes death. Cancer involves abnormal and autonomous cell growth with potential danger. Cancer cells are carried to the other parts of the body by circulation, where they develop further. This disease caused by various agents such as radiant energy, chemical substances and due to genetic factors. The anticancer drugs which are used in the treatment of this disease act either by modify the growth or killing the cancer cells. Anticancer activity of geiparvarin (a natural coumarin derivative) (Fig. 2) is detailed in literature (Cravotto et al. 2001)

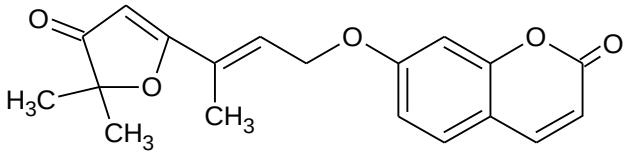


Fig. 2: Structure of Geiparvarin

Conclusion

Above mentioned, review state that coumarin compounds have been widely observed in medicinal chemistry. Coumarins are found as a major class in the plant kingdom. New coumarin derivatives are being discovered or synthesized by various methods in the laboratory. Coumarins exhibit a wide range of biological, pharmacological and physiological profile which leads a strong motivation for more research in this area. As a very large class of compounds coumarins are found in the plant kingdom.

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