DOI: 10.55522/jmpas.v2i3.0019 **ISSN NO. 2320 – 7418**

International peer reviewed open access journal

Journal of Medical Pharmaceutical and Allied Sciences

Journal homepage: www.jmpas.com CODEN: JMPACO

Research article

A review on design, synthesis and pharmacological evaluation of novel coumarins derivatives

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Received - 30 April 2013**, Revised -** 12 May 2013, **Accepted** – 23 June 2013 **(DD-MM-YYYY)**

Refer This Article

Farook Mohd, Ashish Pathak, Nida Khan, 2013. A review on design, synthesis and pharmacological evaluation of novel coumarins derivatives. Journal of medical pharmaceutical and allied sciences, V 2 - I 3, Pages -67 – 72. Doi: https://doi.org/10.55522/jmpas.v2i3.0019.

ABSTRACT

With the aim to find out the structural features for the MAO inhibitory activity and selectivity, in the present communication we report the design, synthesis and pharmacological evaluation review of a new series of 2-H-Chromen-2-one 4- methyl-2H-chromen-2-one Coumarin derivatives without substituent and with different number of methoxy substituent in the 3-phenyl ring, 3,4-dihydrocoumarin. The substituent in this new scaffold was introduced in the 3', 4' and/or 5' positions of the 3-phenyl ring of the coumarin moiety. The synthesized compounds **3-6** were evaluated as MAO A and B inhibitors using **R-(-)-deprenyl** (selegiline) and **Iproniazide** as reference inhibitors, showing, most of them, MAO-B inhibitory activities in the nanomolar range. Compounds **3** (11.05±0.81 nM), **4** (3.23±0.49 nM) and **5** (7.12±0.01 nM) show higher activity than selegiline (IC50 = 19.60 nM), and high MAO-B selectivity with 9,050- fold, 30,960-fold and 14,045-fold inhibition levels, with respect to the MAO-A isoform.

Keywords: Coumarin, MAO-B inhibitor, QSAR approach, therapeutically active.

INTRODUCTION

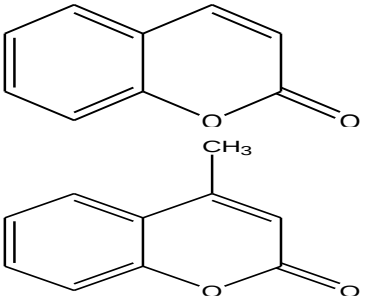
Coumarin comprise a very large class of compounds found throughout the plant kingdom and their natural and/or synthetic derivatives are pharmacologically interesting compounds due to their structural diversity. Due to the synthetic accessibility and substitution variability these heterocyclic compounds play an important role not only in organic chemistry but also in the field of medicinal chemistry.

Coumarin are phenolic substances made of fused benzene and a-pyrone rings they are responsible for characteristic odour of hay. Their fame has come mainly from their anti-microbial, antifungal, antiviral, anti-inflammatory, and anticoagulant activities.

Coumarin (anhydride of o-coumaric acid) is a white lactone, obtainable naturally from several plants, such as Tonka bean, Lavender, sweet clover grass, strawberries and Cinnamon or produced synthetically from an amino acid ,phenylalanine. Coumarin has characteristic odour like that of vanilla beans. It is used for the preparation of flavours and fragrances .the coumarin nucleus (benzo-2-pyrone is derived from cinnamic acid (phenyl acrylic skeleton) in the bio-synthesis. Accordingly, the hydroxyl group attached to coumarin structure at 7 position is important in biosynthesis pathway. Umbelliferone (7-hydroxycoumarin), esculetin (6, 7-Dihydroxycoumarin), Scopoletin (7-hydroxy-6-methoxycoumarin) are the widespread coumarins in nature. Coumarin derivatives are used as therapeutic anticoagulants and as rodenticides by causing fatal hemorrhage synthetic 7-hydroxy coumarin is a widely used fragrance ingredient. It was found in 57% of 73 deodorants on the European market in a 1998 published study coumarin is regulated within the 7th amendment of the Cosmetic directive which required labeling if present in a concentration of 10ppm or higher in leave -on or 100ppm in rinse –off products . There is no upper limit to the concentration of coumarin which may be present in finished cosmetic products according to council directive 76/768/EEc on cosmetics or in the IFRA standard coumarin has caused allergic reaction on 1.2-6.8 of patients suspected for fragrance contact allergy [1].

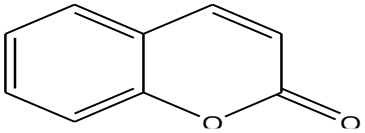
The coumarins are extremely variable in structure, due to the various types of substitutions in their basic structure, which can influence their biological activity. A careful structure-system-activity-relationship study of coumarins with special respect to carcinogenicity, mutagenicity, and cancer-preventing activities should be conducted. Vast majority of coumarins, completely innocuous, may be beneficial in a variety of human disorders, in spite of someongoing controversy.

Structure



2-H-Chromen-2-one 4- methyl-2H-chromen-2-one Coumarin 4-methyl coumarin

Structural Formula: Formula C_9H_6O



Physical Form: Yellowish white crystals,flakes or powder

Molecular Formula: Molecular weight: 146

Solubility: Soluble in alcohol, ether,chloroform and fixed volatile oils; slightly soluble in water

Additional Physical and chemical specifications

Organoleptic Properties:fragrant odour similar to vanilla

Melting Point: 69°C

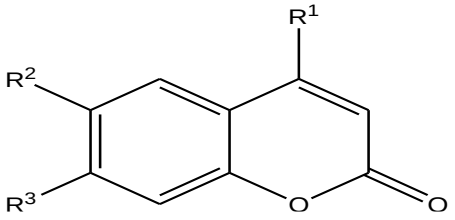
Boiling Point: 290°C

Type of derivative

There are four main coumarin sub-types: the simple coumarins, furanocoumarins, pyranocoumarins and the pyrone-substituted coumarins The simple coumarins (e.g. coumarin, 7-hydroxycoumarin and 6,7-dihydroxycoumarin), are the hydroxylated, alkoxylated and alkylated derivatives of the parent compound, coumarin, along with their glycosides. Furanocoumarins consist of a five-membered furan ring attached to the coumarin nucleus, divided into linear or angular types with substituents at one or both of the remaining benzoid positions. Pyranocoumarin members are analogous to the furanocoumarins, but contain a six-membered ring. Coumarins substituted in the pyrone ring include 4-hydroxycoumarin. The synthetic compound, warfarin, belongs to this coumarin subtype. By virtue of its structural simplicity coumarin has been assigned as head of the benzo-a-pyrones, although it is generally accepted that 7-hydroxycoumarin be regarded as the parent compound of the more complex coumarins.

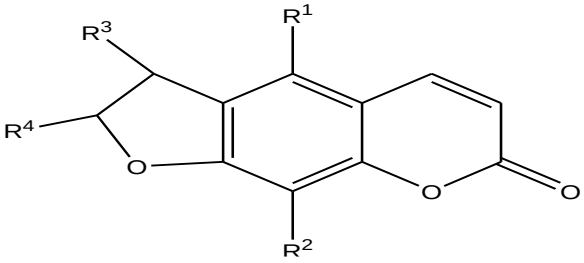
Simple

These are the hydroxylated, aloxylated and alkylated derivatives of the parent compound, Coumarin, along with their glycosides [2].



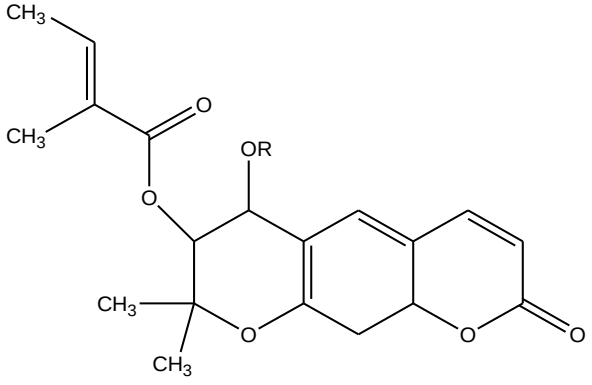
	R^1	R^2	R^3
Coumarin	H	H	H
Herniarin	H	H	OCH_3
Methyl-umbelliferon	CH_3	H	OH
Scopoletin	H	OCH_3	OH
Ostruthin	H	H	OH

Furanocoumarins- These compound consist of a five-membered furan ring attached to the coumarin nucleus,divided to linear and angular types with substituents at one or both of the remaining benzenoid positions.

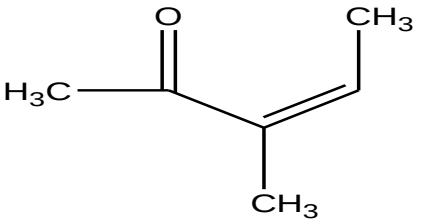


	R^1	R^2	R^3	R^4
Bergapten	OCH_3	H	H	H
Isopimpinelin	OCH_3	OCH_3	H	H
Peucedanin	H	H	OCH_3	$CH(CH_3)_2$
Psoralen	H	H	H	H
Xanthotoxin	H	OCH_3	H	H

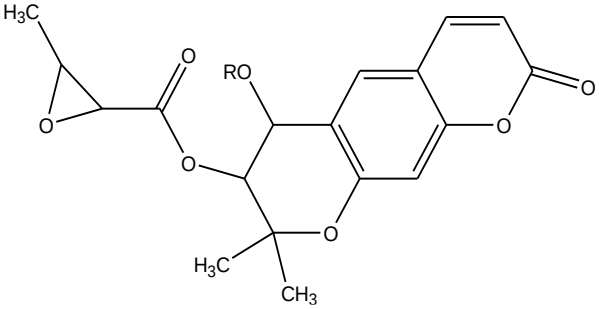
Pyranocoumarins- member of this group are analogous to the furanocoumarins, but contain a six –membered ring.



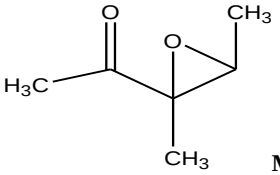
Where R=



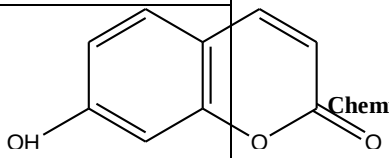
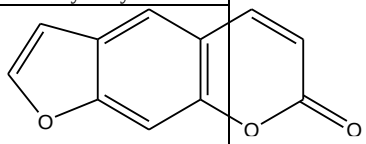
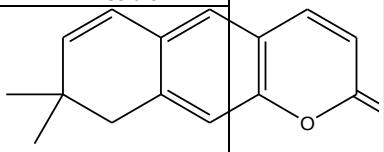
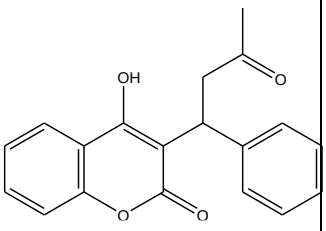
Pyrone-substituted coumarins-



Where R =

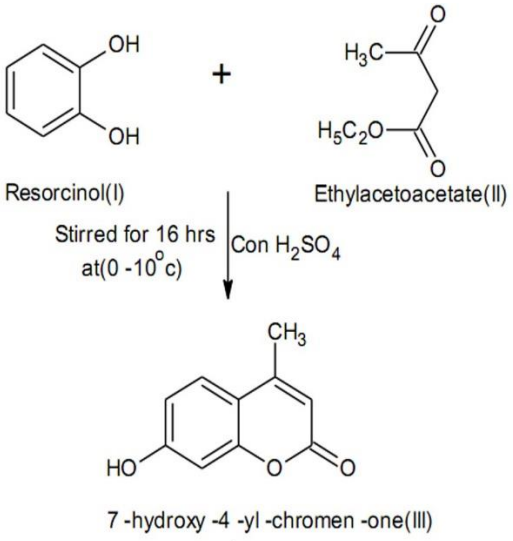


Main Structural feature with Example of Each coumarin subtype

CLASSIFICATION	FEATURES	EXAMPLE
Simple Coumarins	Hydroxylated, alkoxylated or alkylated on benzene ring	 7-hydroxycoumarin
Furano coumarins	5-membered furan ring attached to benzene ring. Linear or Angular	 Psoralen
Pyrano coumarins	6-membered pyran ring attached to benzene ring.Linear or Angular	 Xanthyletin
Pyrone-Substituted Coumarins	Substitution on pyrone ring,often at 3-C or 4-C positions	 Warfarin

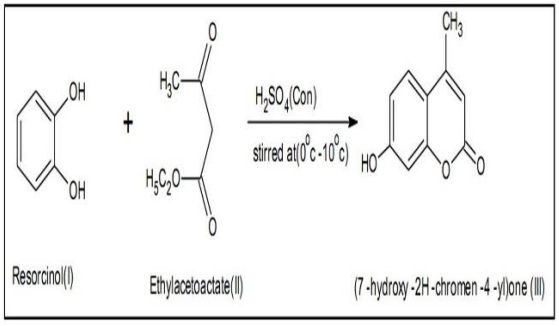
Simple reaction mechanism of basic molecule

Coumarin derivatives can be synthesized by one of such methods as the Claisen rearrangement, Perkin reaction, Pechmann reaction Witting reaction, as well as the Knoevnagel condensation. Derivatives of coumarins usually occur naturally as secondary metabolite present in seed, roots and leaves of many plant species Microwave irradiation has since been proven to be extremely useful for promoting and simplifying many condensation reactions which can be carried out both in solvent and under solvent free condition. The essence of this work was synthesis of coumarin derivatives using microwave irradiation in comparison with conventional methods. These investigations have revealed their potentials as versatile biodynamic agent for example-3-heteroaryl substituted coumarin and benzocoumarins of potential interest as pharmaceuticals and photochromic dyes.



Chemicals

1) Resorcinol:- 33gm (0.01 mole)
2) Ethylacetoacetate: 35ml(0.01 mole)
3) Conc H_2SO_4:- 250 ml



Procedure

In two necked 500ml round bottom flask take 250 ml conc. H_2SO_4 and keep into ice bath until the temperature of solution become (0-10 °C) .After this add solution of resorcinol (I), 33 gm (0.1 moles) and 35 ml (0.01 Moles) of ethyl acetate (II) drop wise with stirring for two hrs,the temperature of solution was maintained below 10°C. After completion of addition the solution stirred for one hr at room temperature and his reaction mixture was stirred for 16 hrs at room temp. After this reaction mixture was added into crushed ice. The yellowish solid separated out which was filtered off and the solid was dissolved into the 5% sodium hydroxide solution and make acidic with 2M H_2SO_4 .the resultant solid was filtered and wash with ice cold water

Spectral characterization

The IR spectra (in KBr) 7-hydroxy-4-methyl Coumarin showed characteristic bands at 1678 cm-1describes the lactone group (C=O), and at 3437 cm-1 describes the hydroxyl group (-OH) [3].

QSAR approaches (design)

SAR descriptions (like functional group are responsible for activity) with structure

Introduction of fluoro and sulfonamide moieties into coumarin side chain hoping for an improvement of biological activity because incorporation of fluorine to various heterocycles is known to influence the biological activity and the sulfonamide moiety itself possesses important antibacterial and antitumor activity.Specifically 1, 5 substituted benzothiazepine are well known compounds for diverse therapeutically properties like antimicrobial , antihypertensive , calcium channel blocker , blood platelet aggregation inhibitory and coronary vasodilatory effects.

Furthermore isoxazoline derivative of coumarins and chalcones possesses antibacterial activity against bacteria (gram+ve) and (gram-ve) and antifungal activity and also 3-bromoacetyl coumarin with thiazo group (Schiff bases) possess a broad spectrum of biological importance .The coumarins containing a Schiff base are expected to have enhanced antitumor and other biological activity [4].

Pharmacological applications

Applications of Coumarin and Coumarin Derivatives

The coumarins are of great interest due to their biological properties. In particular, their physiological, bacteriostatic and anti-tumour activity makes these compounds attractive for further backbone derivatisation and screening as novel\ therapeutic agents. Weber and co-workers have shown that coumarin and its metabolite 7-hydroxycoumarin have antitumour activity against several human tumour cell lines. Both coumarin and coumarin derivatives have shown promise as potential inhibitors of cellular proliferation in various carcinoma cell lines, In addition it has been shown that 4-hydroxycoumarin and 7-hydroxycoumarin inhibited cell proliferation in a gastric carcinoma cell line [5].

Anticoagulant Activity

Coumarins for Anticoagulant Activity. Dicoumarol exhibited anticoagulant activity.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).Vitamin K is a cofactor for the post translational Carboxylation of glutamate residues to ϒ-carboxyglutamates On the N-terminal regions of vitamin K-dependent proteins.

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

Vitamin K conversion cycle, thereby causing hepatic production of partially carboxylated and decarboxylated proteins With reduced procoagulant activity.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 exerta procoagulant effect.In the presence of calcium ions, carboxylation causes a conformational change in coagulation proteins that promotes binding to cofactors on phospholipid surfaces [7].

Hecarboxylation reaction requires the reduced form of Vitamin K (vitaminKH2),molecular oxygen, and carbon Dioxide and is linked to the oxidation of vitamin KH2 to Vitamin K epoxide.Vitamin K epoxideis then recycled to vitamin KH2 throught two reductase steps .The first, which is sensitive to vitamin K antagonist reduces vitamin K epoxide to vitamin K1 (the natural food form of vitamin K1),while the second, which is relatively insensitive to vitamin K antagonists,reduces vitaminK1 to vitamin KH2.Treatment with vitamin K antagonists leads to the depletion of vitamin KH2,the re by limiting the carboxylation of vitamin K-dependent coagulant proteins. The effect of coumarins can be counteracted by vitamin K1 because these Second reductase step is relatively in sensitive to Vitamin K antagonists. Patients treated with a large dose of vitaminK1 can also become warfarin resistant for up to a week because vitamin K1 accumulates in the liver and is available to the coumarin-insensitive reductase.

Antimicrobial Activity

Some Coumarin substituted at 7^{th} and 8^{th} position by using different drugs like aromatic aldihyde to form shiffs bases, and 4-chlorodinitrobenzene,4-chlorobenzonitrile ,4-fluroaniline,dibromoethane.since the many synthesisized compound excibit potent anti-bacterial activity as comparable with the standard employed ,it is desirable to determine their toxicity to decide on whether to go for further screening or not.

Cytotoxic Effect

Ratanasavanh D. et al. compared the cytotoxic effect of coumarin and its derivatives, 7-hydroxycoumarin, 4-hydroxycoumarin, o-hydroxyphenyl acetic acid and o-coumaric acid, on cultured hepatocytes from human, rat, mouse and rabbit liver. At 10-5 and 5.10-5 M, coumarin and its derivatives did not give rise to any signs of toxicity on cultured hepatocytes of the four species. At 10-4 M, coumarin, but not its derivatives, induced release of lactate dehydrogenase (LDH) into the medium, especially in rat hepatocyte cultures. Intracellular LDH activities were correspondingly reduced. The cytotoxic effect of coumarin in cultured rat hepatocytes was evidenced on morphological examination and from the results of the 3-(4, 5- dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium (MTT) reduction test. At higher concentrations (5 .10-4 M), 7-hydroxycoumarin and o-coumaric acid were also found to be cytotoxic in cultured rat hepatocytes. The cytotoxic effect of coumarin (5.10-4 M) was decreased in the presence of SKF 525-A, a cytochrome P450 inhibitor. Interspecies comparisons showed that rat hepatocytes were the most sensitive to the toxicity of coumarin and its derivatives, whereas human hepatocytes were the most resistant. The results suggest that the cytotoxicity of coumarin is metabolism and species

dependent. Thus, the rat may not be a suitable model for evaluating the pharmacological hazards of coumarin in humans [8].

Anti-inflammatory and analgesic activity

Coumarins can reduce tissue edema and inflammation and inhibit prostaglandin biosynthesis, which involves fatty acid hydroperoxy intermediates. It is to be expected that coumarins might affect the formation and scavenging of reactive substances derived from oxygen species (ROS) and influence processes involving free radical-mediated injury, as can flavonoids.

During a small number of (Q) SAR studies concerning coumarins as NSAIDs has been presented and reviewed. Examine the structure-function relationship for coumarins, presenting antiinflammatory activity. Coumarin, the prototypical compound presents anti-inflammatory activity. The hydroxylaromatic substituted derivatives (5- or 6- or 7-hydroxy or the vicinal dihydroxy) seems to be potent inhibitors of lipoxygenase. Several synthetic derivatives simple or more complicated were found to be potent antiinflammatories/antioxidant agents [9].

Antioxident activity

The free radical scavenging activities of Coumarin Derivatives are related to the number and position of the hydroxyl group on the benzenoid ring of the coumarin system. Moreover in hydroxylated coumarin, the substituent at C-2, C-4, C-7 positions is reported to play a key role in enhancing the activity. In findings agreement with the hydroxyl substitutions, was observed that the 4-hydroxy substituted Coumarin Derivatives (C8) and 7-hydroxy substituted CoumarinDerivatives such as C5, C6 and C7 have demonstrated significant DPPH radical scavenging activity as compared to remaining selected Coumarin Derivatives.

While describing the mechanism of free radical scavenging activities of the Coumarin Derivatives, it has been reported that the coumarins possessing hydroxyl groups directly recombine with free radicals and interrupt the initiation and/or propagation of the induced chain reactions. As a result of the phenolic behaviour of the Coumarin Derivatives,they are also reported to act as potent metal chelators and free radical scavengers, thereby showing a powerful antioxidant effect. To show antioxidant activity, a coumarin derivative has to possess at least one hydroxyl group.

The HOMO and LUMO orbital energies are closely associated with the free radical scavenging activities of the antioxidant molecules. The energy of the HOMO is directly related to the ionization potential and indicates the susceptibility of the molecule to attack by electrophiles. However, the energy of the LUMO is attributed to the electron affinity and signifies the susceptibility of the molecule toward attack by nucleophiles.

Conceptually, the nucleophiles and electrophiles have close attributes with radical scavenging activities manifested under the relative energy influence of the HOMO/LUMO orbitals. Nucleophiles (electron donors) and electrophiles (electron acceptors) have a high-energy HOMO and low-energy LUMO respectively. Electron-donating atoms possess high HOMO with a loose holding of valence electron, thereby being susceptible to oxidation.Substances with low ionization energy give up electrons easily and hence are likely to participate in chemical reactions. In the present studies HOMO/LUMO energy profiles of the most promising DPPH radical scavenging Coumarin Derivatives such as C6, C7, C5 and C8 do not show higher HOMO as compared to other Derivatives. However, it is interesting to note that these compounds have more or less equal HOMO energy (−9.1 or −9.2 eV). Classically, the dipole moment (DM) of a substance indicates its polarity. It has been described that the solubility of a drug substance in water increases with an increase in DM and SASA. With few exceptions, the DM and the SASA calculated for the active Coumarin Derivatives like C6, C7, C8 and C5, to a greater extent are in agreement with the DPPH radical scavenging activity.

Anti-parkinsonism activity

MAO inhibitory activity 7substituted Coumarin derivatives in which the activity and selectivity can be modulated depending of t he substituents in the pyrone ring. Starting from these studies, in t he last years research has carried out the synthesis of different 3-arylcoumarins with an interesting MAO-
B inhibitor activity. On basis of that, we can conclude that substituent s in the 7-position are not essntials for the MAO-
B inhibition, if in the 3-position of the coumarin an aryl group is present.

This results encouraged us to produce a series of 3-arylcoumarin where a hydroxyl group have been incorporated at the 4 position of the coumarin scaffold. We also pretend to introduce su bstituents in one or two aromatic rings with different electronic, steric and/or lipophilic properties in order to study the effects on the possible activity and/or selective MAO-A/B.

Coumarin in Lukemia

The effect of coumarin and 7-hydroxycoumarin on the cell cycle and its regulatory molecules has been investigated. The cytostatic and cytotoxic nature of 8-nitro- 7-hydroxycoumarin (8-NO2-7-OHC) was determined using both human and animal cell lines grown in vitro. This compound displayed cytotoxic properties in two human cell lines tested (HL-60 and K562), inducing cell death by apoptosis. This compound imposed a cytostatic effect on the three other cell lines tested, exerted through a perturbation in their cell cycle.The effect of a number of coumarin compounds on the growth, metabolism and cell signalling of human tumour cell lines was examined by Cooke. Overall esculetin exhibited the strongest antiproliferative effect on the carcinoma cell lines tested. Given the importance of signalling anomalies in cancer cells, tests were

performed to determine if the cellular target of 7-hydroxy- coumarin was a signalling pathway component. Both 7- hydroxycoumarin were found to inhibit tyrosine phosphorylation in EGF-stimulated tumour cells in a time- and dose-dependent manner. It appears that this effect may be achieved by reduction of the tyrosine kinase activity of the EGF-Receptor [10].

High Protein Oedema

Coumarin and numerous other benzopyrones have been tested in high protein oedema, and all have been shown to successfully reduce the swelling. However, according to Loprinzi and colleagues, coumarin treatment alone is not effective therapy for women who have lymphoedema of the arm after treatment for breast cancer. It may be possible to increase the beneficial therapeutic effect of coumarin by using it with other compounds in combination treatments. The objective of a recent study was to evaluate the oedema-protective effect of a combination vasoactive drug, coumarin/troxerutin (SB-LOT) plus compression stockings in patients suffering from chronic venous insufficiency after decongestion of the legs as recommended by the new guidelines. The study confirms the oedema-protective effect of SB-LOT in chronic venous insufficiency and provides a treatment option for patients who discontinue compression after a short time.

CONCLUSION

Coumarin and coumarin-related compounds have proved for many years to have significant therapeutic potential. They come from a wide variety of natural sources and new coumarin derivatives are being discovered or synthesised on a Regular basis. Coumarin is a simple molecule and many of derivatives have been known for more than a century.However, their vital role in plant and animal biology has not been fully exploited. Coumarins have multiple biological activities including disease prevention, growth modulation and anti-oxidant properties. These compounds are known to exert anti-tumour effects and can cause significant changes in the regulation of immune responses, cell growth and differentiation. Research involving coumarins and their effect on, antimicrobial, anticouagulant, anti-inflammatory, anti-parkinsonism activity and cytotoxic effect are discussed in this review.

In order to give an overview of the various potential therapeutic applications of coumarins. It is evident from the research described that coumarin and coumarin-related compounds are a plentiful source of potential drugs deserving further study.

Acknowledgement

The authors are very grateful to Mr. Dinesh Bajpai (Research associate), for her persistent creative encouragement and valuable guidance throughout the research work.

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