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Review article

Antioxidant Activity of Coumarins

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ABSTRACT
Coumarins are heterocyclic molecules that have been associated with beneficial effects on human health, such as reducing the risk of cancer, diabetes, cardiovascular and brain diseases. These effects are thought to be related to the radical scavenging effect, due to their antioxidant activities. Coumarins are an entity which is being synthesized in many of its derivative from past few years; the entity is major source of interest for many of medicinal chemist to explore its various pharmacological potentials especially anticoagulant activity. In present article we review recent derivatives of coumarin that are synthesized with their pharmacological activities like antioxidant, activity. The main purpose of this review is to summarize recent chemical syntheses and structural modifications of coumarin and there derivatives, of interest due to their characteristic conjugated molecular architecture and biological activities.

Key words: Coumarin, Antioxidant activity, Umbelferone, DPPH.

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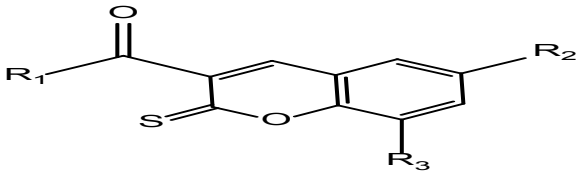
INTRODUCTION

Antioxidants in food play an important role as a health-protecting factor. Scientific evidence suggests that antioxidants reduce the risk for chronic diseases including cancer and heart disease. Primary sources of naturally occurring antioxidants are whole grains, fruits and vegetables. Plant sourced food antioxidants like vitamin C, vitamin E, carotenes, phenolic acids, phytate and phytoestrogens have been recognized as having the potential to reduce disease risk. Most of the antioxidant compounds in a typical diet are derived from plant sources and belongs to various classes of compounds with a wide variety of physical and chemical properties. Some compounds, such as gallates have strong antioxidant activity, while others, such as the mono-phenols are weak antioxidants. Coumarin and its derivatives represent one of the most active classes of compound possessing a wide spectrum of biological activity.[1–4] Many of these compounds have proven to be active as antibacterial,[5–7] antifungal,[8] anti-inflammatory,[9] anticoagulant,[10] anti-HIV[11] and antitumor agents.[12] Coumarins are widely used as additives in food, perfumes, cosmetics,[13] pharmaceuticals and optical brighteners[14] and would dispersed fluorescent and laser dyes.[15] Coumarins also have the super thermal stability and outstanding optical properties including extended spectral response, high quantum yields and superior photo stability. Optical applications of these compounds, such as laser dyes, nonlinear optical chromophores, fluorescent whiteners, fluorescent probes, polymer science, optical recording and solar energy collectors have been widely investigated.[16–20] Classical routes to coumarins incorporate Pechmann, Knoevenagel, Perkin, Reformat sky, and Wittig condensation reactions.[21–24] To make these classical reactions efficacious, several variations in terms of catalyst and reaction conditions have been introduced.25,26 Now when coumarin ring fused with other rings showing a synergistic effect of both the rings in their biological activities are obtained. Such compounds are exploited in development of various important molecule which provides scaffolds for drug development. Various moieties when combined with coumarin can produces same or different effects but with different potencies.27
In continuation of previous studies[28–37] on coumarins, herein we are reporting a review for such recent derivatives of coumarins with antioxidant activities.

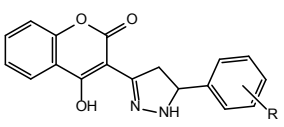
Antioxidant Activity

Singh OM *et al.* developed a facile, convenient and high yielding synthesis of a combinatorial library of 3-alkanoyl/aroyl/heteroaroyl-2H-chromene-2-thiones (1). The assessment of radical scavenging capacity of the compounds towards the stable free radical 2,2-diphenyl-1- picrylhydrazyl (DPPH) was measured and these compounds were found to scavenge DPPH free radicals efficiently. The newly synthesized compounds exhibited profound antioxidant activity. Five selected compounds were able to protect curcumin from the attack of sulphur free radical generated by radiolysis of glutathione (GSH).[38]



(1)

R_1= substituted phenyls, hetrocyclic nuclei / R_2= -H, -Br / R_3= -H, -OCH_3
Abdullah S *et al.* synthesized a series of coumarin derivatives (2,3) and these compounds were evaluated for their *in-vitro* antioxidant activity and *in-vivo* anti antibacterial activity. These derivatives were found to possess the mentioned activities and on the basis of results, structure activity relationships (SAR) were developed in order to define the structural features required for activity.[39]



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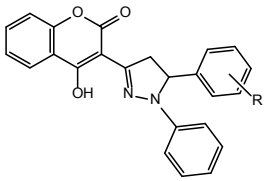

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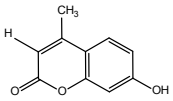
Ravi. S *et al.* synthesized three derivatives of 4-methyl chromen- 2-one-compounds (4,5,6) .Their antioxidant activity were expressed as IC50 with different antioxidant. The calculated values for three 4- methyl chromen- 2-one derivatives and using callic acid as reference were (2.04 µg/

ml,1.98 µg/ml, 15.0698 µg/ml, 0.0298 µg/ml for DPPH method), (3.72 µg/ml, 43.57 µg/ml,40.13 µg/ml,0.28µg/ml for nitric oxide method).[40] The antioxidant study was also carried out by using phosphor molybdenum assay method, showed that the test samples had good antioxidant activity. Free radical scavenging activity of the coumarin compounds is concentration dependent. The concentration of the test compounds increases, the radical scavenging activity also increases and lower IC50 value reflects better protective action. The anti-oxidant activity of these 4-methyl chromen-2-one derivatives could be attributed to electron donating nature of the substituents like -OH, $-CH_3$, $-C_6H_5$ on coumarin scaffold, which reduce free radicals and prevent the damage of cell. The more the hydrogen donors, the stronger is the anti-oxidant activity.[41,42]



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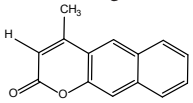

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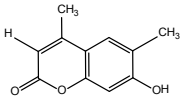

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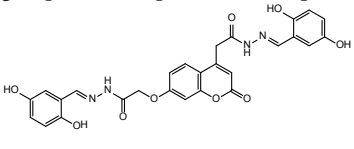
Maja. M *et al*. synthesized a series of coumarin derivatives compounds (7,8,9,10).These compounds were evaluated for their *in-vitro* antioxidant activity.[43] These compounds contain 3,4-dihydroxyphenyl and 2,5-dihidroxyphenyl ring with these substituents. The compounds was expected to possess antioxidant activity since hydrogen donation leads to formation of a stable quinoid structure. It has been reported that two hydroxyl groups in ortho position are important for antioxidant activity.[44-46]



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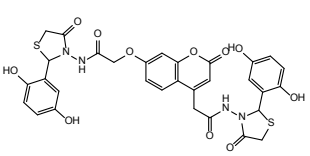

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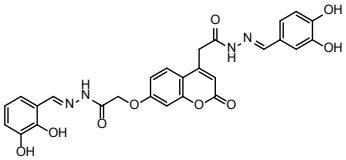

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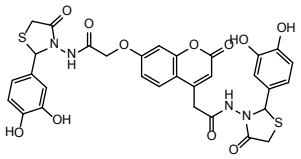
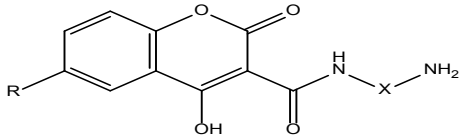


(10)

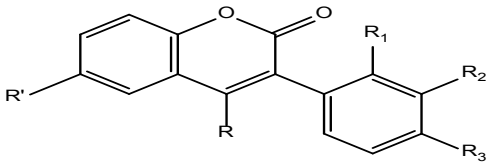
Melagraki .G *et al*. synthesizeda series of novel coumarin-3-carboxamides (11) and the synthesis compounds were evaluated for their *in-vitro* antioxidant activity and *in-vivo* anti-inflammatory activity. These derivatives were found to possess the mentioned activities and on the basis of results, structure activity relationships (SAR) were developed in order to define the structural features required for activity.[47]



(11)

R= -H, $-CH_3$ / X= $-(CH_2)_2$,$-(CH_2)_6$

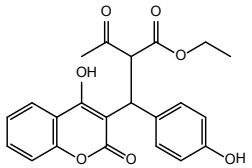
Roussaki M *et al*. Synthesized a series of coumarin analogues (12) bearing a substituted phenyl ring on position 3. *In vitro* antioxidant activity of the synthesized compounds was evaluated using two different antioxidant assays. Ability of the compounds to inhibit soybean lipoxygenase was also determined as an indication of potential anti-inflammatory activity.[48]



(12)

R= -H ,$-CH_3$/ R'= -H ,-Cl, -Br / R_1=-H ,-Br, $-OCH_3$ / R_2=-H ,$-OCH_3$/ R_3= $-OCH_3$, $-NO_2$,-OH ,-Br ,-H

Stanchev S *et al*. synthesized four 4-hydroxycoumarin derivatives (13,14,15,16). These compounds were tested for *in vitro* antioxidant activity in hypochlorous system. The assay was based on the luminal-dependent chemiluminescence of free radicals, which decreased in the presence of 4-hydroxycoumarin derivative compound (16) expressed the best scavenger activity at the highest concentration (10–4 $molL^{-1}$).[49]



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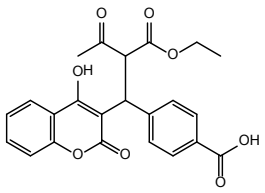

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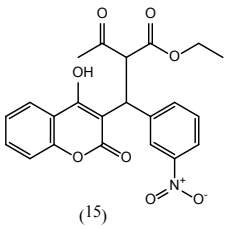

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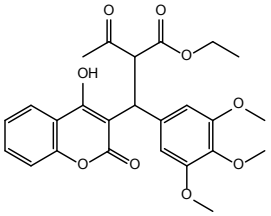
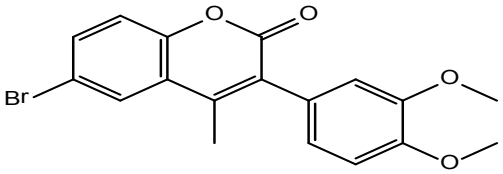


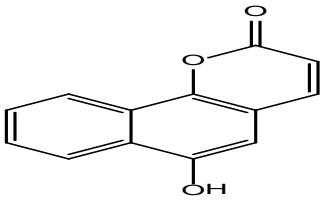
(16)

Per-oxidation activity, substituent on the aromatic ring of the benzopyranone moiety, the presence of electron-withdrawing groups on the phenyl ring of position 3 favours activity. The best combined pharmacological profile is exhibited by compound 17.[50]



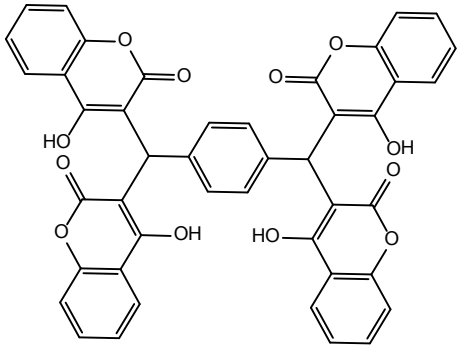
(17)

Substituted hydroxycoumarins and 7- or 8-hydroxybenzo (f) coumarins were prepared by the treatment of phenols and naphtha lenediols, respectively, with malic acid and H_2SO_4 under microwave irradiation. It has been identified that phenolic compounds present antioxidant activity. The presence of the phenolic hydroxyl group (6-, 7- or 8-) seems to support the antioxidant activity but the effect on activity is independent of the position of hydroxyl group. It is generalized that the benzo derivative compound 2 is more potent than any of the cyclohexyl derivatives. Compound (18) shows higher antioxidant activity among various hydroxybenzo coumarins being synthesized.[51]



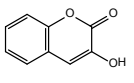
(18)

Different substituted 3, 3'-arylidenebis-4-hydroxycoumarins and tetrakis-4-hydroxycoumarin derivative (compound 3) were synthesized by 4-hydroxycoumarin and aromatic aldehydes containing different groups in ortho, Meta or para positions and condensing them in boiling ethanol or acetic acid. A possible relationship between intermolecular hydrogen-bonded structures and the antioxidant activities of these compounds are analyzed . The compounds which contain intermolecular hydrogen bonds is uncoupler and inhibitor of mitochondrial oxidative phosphorylation, while compounds which can only form intermolecular hydrogen bonds, is only uncoupler of oxidative phosphorylation. Thus, the formation of hydrogen bonds may be an important factor in assisting the synthesized dicoumarols (specifically compound 19) to attain the correct configuration for antioxidant activities.[52]



(19)

Rajesh n*et al*. Synthesized a series of coumarin derivatives and these compounds were evaluated for their *in-vitro* antioxidant activity and *in-vivo* anti anticancer activity, The newly synthesized compounds exhibited profound antioxidant activity and The presence of the phenolic hydroxyl group seems to support the antioxidant activity.[53]



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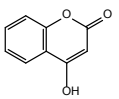

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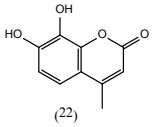

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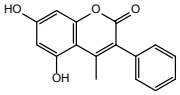
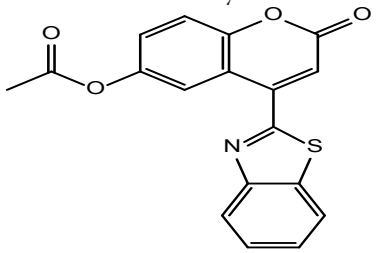


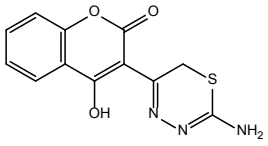
(23)

Shivani Ch *et al*. Synthesized new coumarin substituted derivatives of benzothiazole and they were evaluated for antioxidant activity by DPPH radical scavenging activity. The test compound (24) showed good in-vitro antioxidant activity.[54]



(24)

Milan Ca *et al*. Synthesized a series of newly di-substituted and tri-substituted 1,3,4-thiadiazines with various substituents was prepared utilizing different thiosemicarbazides and 3-α-bromoacetylcoumarins as starting compounds. All of the new thiadiazine derivatives were tested for their antioxidant activity, employing different antioxidant assays (DPPH scavenging activity, iron chelating activity, power reducing activity). Compounds 25,26,27 and 28 were proven to be the best DPPH radical scavengers.[55]



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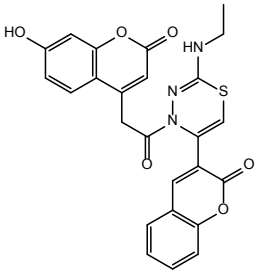

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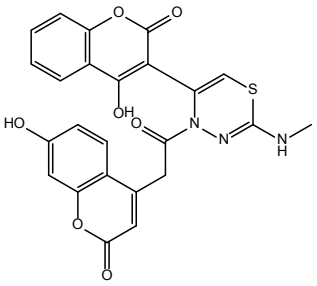

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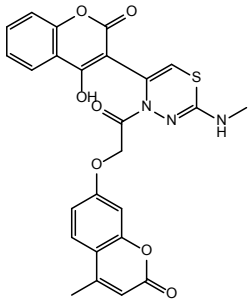
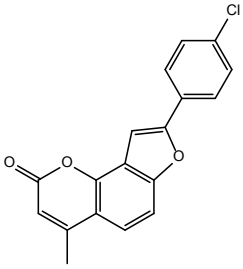


(28)

Y. Sri Ranganath *et al* .synthesized coumarine derivatives by reacting different para substituted acyl bromides with 4-methyl-7-hydroxy coumarin followed by cyclization in acidic medium. These compounds were screened for free radical scavenging activity by DPPH method and preliminary cytotoxic activity by using Ehrlich Ascites Carcinoma cells and Tryptan blue dye exclusion method. Among the compounds tested for radical scavenging and cytotoxic studies, 29 and 30 showed appreciable results when compared with the standard drugs ascorbic acid and 5- flurouracil respectively.[56]



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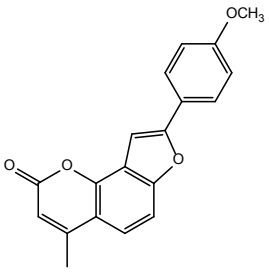

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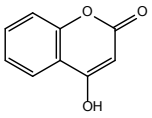
Patel R. *et al*. Synthesized a series of coumarin derivatives compounds (31,32,33)these compounds were evaluated for their *in-vitro* antioxidant activity by DPPH free radical scavenging method, Super oxide method and Nitric oxide method. The value was determined for each compound From results of DPPH, Super oxide and Nitric oxide methods, it found that compound 31 and 32 displayed strong antioxidant activity compared to the ascorbic acid and compound 33 is also showed good antioxidant activity.[57]



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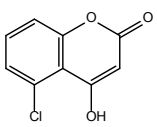

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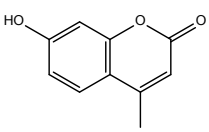
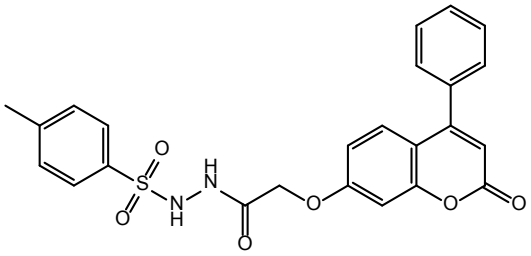


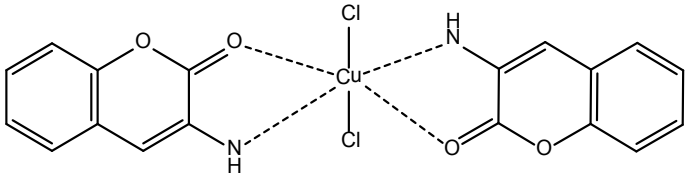
(33)

Mahmoud M *et al*. Synthesizeda novel series of compounds containing coumarinyl moiety derivatives from 2-(2-oxo-4-phenyl- 2H-chromen-7-yloxy)-acetohydrazide and evalution the antioxidant activity. The effect of the different synthetic compounds on DPPH radical scavenging was compared to ascorbic acid using as positive control and appreciated by the determination of the IC 50 values, it found that compound 34 displayed strong antioxidant activity.[58]



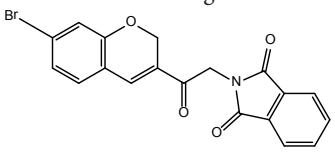
(34)

Abdul A. *et al*. Synthesized 3-Aminocoumarin as aligand (L)for the formation of Cr(III), Ni(II), and Cu(II) complexes. Then determined the free radical scavenging activity of metal complexes by measuring their interaction with the stable free radical DPPH and all the compounds have shown encouraging antioxidant activities. Compound (35) is also found to be a superior antioxidant complex as compared to ascorbic acid.[59]



(35)

Rajasekaran S. *et al*. A series of some coumarinyl and chromensulfanyl derivatives have been synthesized by conventional methods and *in vitro* antioxidant activity by 1,1- Diphenyl-2,2-picryl hydrazyl free radical (DPPH) method and compounds 36,37 were proven to be the best DPPH radical scavengers.[60]



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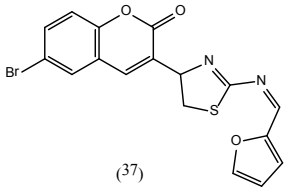
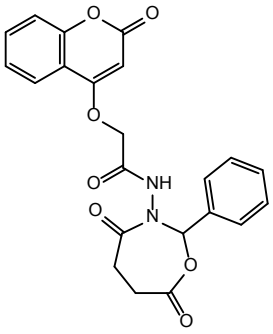
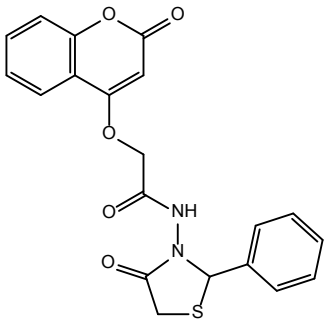


(37)

Abdul A.*et al*. synthesized two coumarins namely, N-(4,7-dioxo-2-phenyl-1,3-oxazepin-3(2H,4H,7H)-yl)-2-(2-oxo-2H-chromen-4-yloxy) acetamide(38) and N-(4-oxo-2-phenylthiazolidin-3-yl)-2-(2-oxo-2H-chromen-4-yloxy)acetamide (39) then study the compounds with the DPPH, hydrogen peroxide and nitric oxide radical methods and compared with the known antioxidant ascorbic acid. Compounds (38) and (39) were displayed strong antioxidant activity.[61]

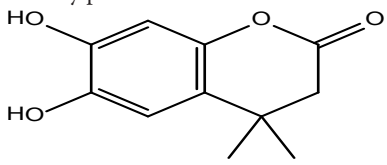


(38)



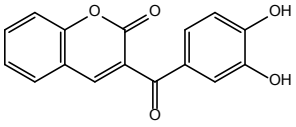
(39)

Nishiyama .T *et al*. Compared the antioxidative activities of seven hydrocoumarins with those of alphatocopherol for the oxidation of tetralin and linoleic acid in a homogeneous solution. Hydro coumarins exhibited a higher induction period than that of alpha-Toc in both systems. However, the rate of oxygen absorption during the induction period for alpha-Toc was slower than that of the hydro coumarins in both systems. In addition, 6,7-dihydroxy-4,4-dimethylhydrocoumarin (40) showed less cytotoxicity toward human fibroblasts than did 2, 6-di-t-butyl-4-methylphenol.[62]

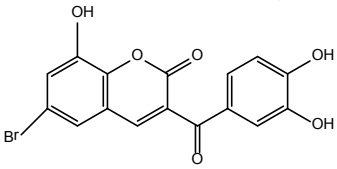


(40)

Saleta V *et al*. we have confirmed the considerable antioxidant activity of new hydroxylated coumarin-chalcone hybrid compounds 41-44 Their antioxidant activity is affected by the introduction of a benzoyl moiety at the C3 position regarding to the coumarin ring. A very interesting finding is that compound 41 is very reactive and presents good antioxidant capacity against hydroxyl and peroxyl radicals as well as low oxidation potential. In spite of the moderate trypanocidal activity of coumarin-chalcone hybrids, they have been proved to be very good antioxidants. Based on these results, we can conclude that compounds 42 and 43 are potential candidates for *in vitro* studies of their antioxidant activity.[63]



(41)



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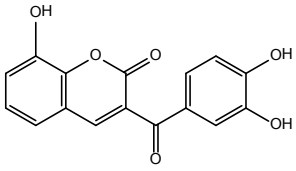

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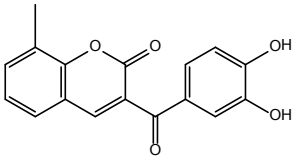
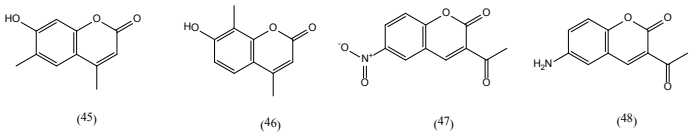


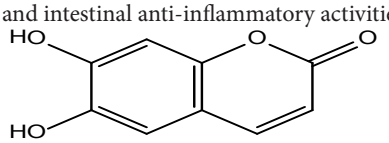
(44)

Jayashree B.S. *et al*. Synthesized novel coumarin analogues, the synthesized compounds have shown free radical scavenging activity by DPPH and Nitric oxide scavenging activity and none of the compounds shown effective antidiabetic activity.[64]



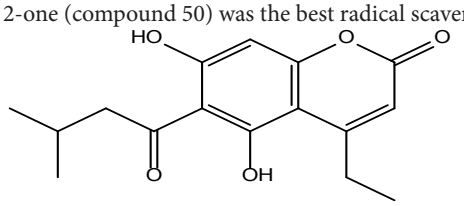
(45) (46) (47) (48)

Witaicenis *et al*. showed that treatment with esculetin (compound 49) and 4-methylesculetin prevent the colonic damage induced by tri nitro benzene sulphonic acid (TNBS) in rats and also that the presence of methyl group at C-4 in the esculetin molecule improves its antioxidant and intestinal anti-inflammatory activities.[65]



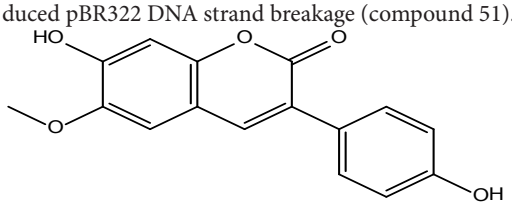
(49)

Chang *et al*. demonstrated that 7- hydroxyl coumarin (umbelliferone) plays a very important role in XO inhibition. Furthermore, some 5,7-dihydroxycoumarins could significantly suppress signals generated by the X/XO system at a low concentration (20 mM) and, among them, the compound 5,7-dihydroxy-6-(3-methyl-butyryl)-4-ethyl- chromen-2-one (compound 50) was the best radical scavenger.[66]



(50)

Yang *et al*. Reported that most hydroxylated 3- phenyl coumarins (stilbene-coumarin hybrids) are effective antioxidants against AAPH-induced pBR322 DNA strand breakage (compound 51).[67]



(51)

Natella *et al*. The presence of the ethoxy carbonylethyl group in DHMC at C-3 position significantly enhanced the antioxidant activity,[68] while the introduction of an ethoxy carbonyl methyl had no influence on it. On the other hand, On the other hand, Kancheva et al.[69] suggested that the substitution at the C-3 position did not have any effect either on the chain-breaking antioxidant activity or on the radical scavenging activity of the 7,8-dihydroxy- and 7,8- diacetoxy-4-methylcoumarins. Recently, Rodríguez et al.[70] showed that the presence of the 3-aryl substituents is crucial for the increased activity and provides the most active radical scavengers.

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 synthesized on a regular basis. Coumarin is a simple molecule and many of its derivatives have been known for more than a century. However, their vital role in plant and animal biology has not been fully exploited. It is evident from the research described that coumarin and coumarin-related compounds are a plentiful source of potential drugs candidate in relation to its safety and efficacy. This review summarized the antioxidant activities of coumarin derivatives.

ACKNOWLEDGEMENT

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CONFLICT OF INTEREST

The authors have declared that no competing interests exist.

ABBREVIATION USED

DPPH: 2,2-diphenyl-1- picrylhydrazyl; **HIV:** human immunodeficiency virus; **SAR:** Structure activity relationships; **IC50:** The half maximal inhibitory concentration; **L:** Ligand; Chrome (Cr), Nickel (Ni), and Copper (Cu); **TNBS:** Trinitrobenzene sulphonic acid (TNBS); **DNA:** Deoxyribonucleic acid; **X/XO:** Xanthine oxidase; **ROS:** Reactive oxygen species; **O_2-:** Superoxide.

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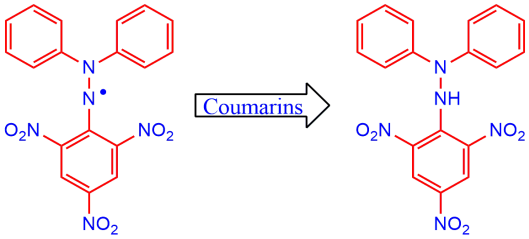
GRAPHICAL ABSTRACT



SUMMARY

- Coumarins have significant therapeutic potential. Coumarins are known for more than a century. Coumarins are a plentiful source of potential drugs candidate in relation to thier safety and efficacy. This review summarized the antioxidant activities of some synthesized coumarins.

AUTHOR PROFILE

Ahmed Al-Amiery: (h-index= 17), is an Professor at University of Technology. Dr. Al-Amiery has over 100 scientific papers and projects either presented or published and international patent. He is an internationally expert in many areas of applied chemistry. Recent publications include a paper on the use of novel coumarin derivatives as corrosion inhibitors. Al-Amiery has Post-doctoral from Department of Chemical and Process Engineering Universiti Kebangsaan Malaysia. Dr. Al-Amiery has been awarded the Medal of scientific excellence (2014), and also Hold Science Day Awards from the Ministry of Higher Education and Scientific Research for four consecutive years (2010-2015). Al-Amiery selected for the Who's Who for International Executives 2015. Al-Amiery is a TWAS-Young Affiliates.