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A REVIEW ON COUMARIN: SAR, SIGNALING PATHWAY (S) IN PHARMACOLOGICAL ACTIVITY & METABOLITE INCUDED-TOXICITY

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ABSTRACT

Coumarin is described as alpha-benzopyrones. Some novel coumarin subsidiaries have been synthesized or confined from regular points. Coumarin is found as white crystalline solid and smell like vanilla. Wang and collaborators synthesized a chain of bifunctional platinum complexes (1-4) with 7-hydroxycoumarin moieties in 2019 and tested them for anticancer efficacy. This review consists an extensive survey of literature from the Scopus, Elsevier, PubMed, Springer Nature and other international reputed sources. This review was focused to unfold the facts of Coumarins & analogues in terms of their chemistry, structure activity relationship (SAR), underlying signalling pathway (s) in pharmacological effects and metabolites induced- toxicity. They are frequently available in different eatables including celery, clover-sweet, strawberry and lavender. Various signalling pathway (s) including lowering oxidative damage, Carbonic Anhydrase Inhibition, Microtubule polymerization inhibition, Reverse Transcriptase (RT) & Protease Inhibition (PI) as anti-diabetic, anticonvulsant, anticancer and anti-viral respectively. In recent years, coumarins got special concern of researchers because of their numerous pharmacological profiles i. e. lowering hyperlipidaemia, tyrosinase inhibition, reducing convulsion, in Parkinson, hepatitis, coagulation, blocking of acetylcholinesterase and Vaso-relaxation. Toxicity includes allergic reactions, facilitating synergism of warfarin effects in individuals. In Conclusion, coumarins are so effective pharmacologically and therapeutically in terms of various healing properties including cancer, Alzheimer, Parkinson etc. In 2021, researchers evaluated coumarins in enzyme mimicking and enzyme inhibition complexes formation. Furthermore, recent breakthroughs in the production of metal complexes with coumarin-based ligands have resulted in probes or sensors that can detect a variety of biological analytes under physiological settings. In order to subside their toxicity, researchers need to modify structural configuration to enhance potential. Coumarins have been researched for possessing various novel properties as discussed above and may promising ones.

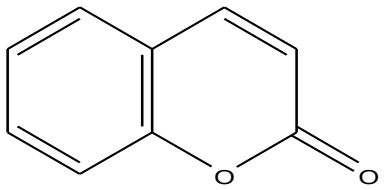
Keywords: Coumarins, signaling-pathway (s), pharmacological activity, toxicity

INTRODUCTION

Coumarin is described as alpha-benzopyrones. Some novel coumarin subsidiaries have been synthesized or confined from regular points. In recent years, coumarins got special concern of researchers because of their numerous pharmacological profiles i. e. lowering hyperlipidaemia, tyrosinase inhibition, reducing convulsion, in Parkinson, hepatitis, coagulation, blocking of acetylcholinesterase and Vaso-relaxation. Coumarin can be also be used as alpha glucosidase, tyrosinase, against wound worms and Mono-Amino Oxidase inhibitors [1]. Coumarins belongs to the benzopyrones family. They are normally plant-determined and artificially taken polyphenolic substances, introducing a wide assortment of biological potentials and practices, supporting their utilization as therapeutic agents for numerous diseases [2]. Coumarins belong to naturally occurring benzopyrone analogue available in herbs in free and as glycosides. They demonstrate numerous pharmacological potentials like antiseptic, anti-carcinoma, anti-hypertension and anti-nociceptive and toxicity shows i. e. phototoxic & carcinogenic [3].

Chemistry of Coumarins

Coumarin is found as white crystalline solid and smell like vanilla. They are frequently available in different eatables including celery, clover-sweet, strawberry and lavender [3]. Wang and collaborators synthesized a chain of bifunctional platinum complexes (1-4) with 7-hydroxycoumarin moieties in 2019 and tested them for anticancer efficacy. Although coumarin, iso-coumarins and their analogues may retain in the body. Coumarins are widely available in plants of higher class as novobiocin. It has been refined from the bacteria and fungus. Among the dicotyledoneous species, the plants belonging to family-Apiaceae, Rutaceae, & Moraceae have shown rich sources of coumarin. A great number of these plants are extensively used as vegetables and spices in terms of nutrition and medicine [4].



Coumarin *IUPAC name:* 2H-chromen-2-one

Molecular formula: C9H6O2

Molecular weight: 146.14

Various coumarin consisting plants have been studied against diseases & conditions associated with inflammation. Some coumarins were found as significant COX & LOX inhibitors. Diverse formulations of coumarin are available as Osthol, osthenol that subside inflammation. The di-hydroxylated derivatives are more selective against 5-LOX enzyme. Some coumarins potentially inhibited cyclo-oxygenase enzyme. The 5,7-dihydroxy-4-methylcoumarin was noted as potent coumarin with its COX selectivity (IC50 = μM) [5]. Coumarins are phenolic compounds with wide distribution in the plant species. The coumarins was first confined by Vogel in 1820. The word 'coumarin' originates from a Caribbean word- coumarou for tree-Tonka (Leguminosae). It shows the

characteristic smell of these compounds and botanically was termed once as *Coumarouna odorata Aubl* [6].

From previous years, coumarin got special concerns of scientists as they have exhibited diverse pharmacological potentials such as in inflammation, pain, cancer, ulcer, plasmodial infection, hyperlipidaemic, tyrosinase inhibition, convulsion, Parkinson etc. [7].

Structure Activity Relationship (SAR) of Coumarins

By making some modifications in the configurational settings of coumarin, researchers have developed more sophisticated and novel coumarin analogues with broad extensive applications and high efficiency [8].

The following table depicts the SAR of coumarins at different positions of addition or substitution reactions-

Table 1. SAR & biochemical response of coumarins

Addition/ Substitution (at different position)	Biochemical effect	References
Addition of an electronegative atom; hydrogen bonding	Increased hydrophilicity, Solubility	[9]
The addition of nitro group at C3 position; Nitro & Acetyl group at position- C6 and C7	Antifungal	[10]
The length of the C-ether-chain with N-methyl analogues Substitution of the nitrogenous groups- NH2, NO2 & methoxy at the C6 position Geranyloxy group at C7 position	Anti-Alzheimer	[11]
Addition of cyclopentenyl & alicyclic rings at C3 & C4 positions respectively Phenyl groups at C3 position	Anti-depressant	[12]
Attachment of OH group at C4, C6, and C7 positions Thiosemicarbazide or aryl-substituted thiosemicarbazide at the C7 position	Anti-oxidant	[13]
Substitution of 3-methoxyphenyl group at R	TNF-α inhibitory activity	[14]
Phenyl & 4-hydroxyphenyl replacement at R	IL-6 inhibition	[14]
Umbelliferone 6-carboxylic acid (UMC)	Anti-inflammatory	[15]

Coumarins Toxicity

Coumarin analogues are highly utilized in the scent industry as facilitator and stabilizer. Its toxicity includes allergic reactions, synergism of warfarin and skin-itching in individuals [3]. Some recent studies exhibited that humankind is not more likely to produce toxicity of this metabolite, obtained by highly reactive 3,4-coumarinepoxide and 3-hydroxycoumarin due to comparatively low frequency of coumarin exposures.

Few researches done on zebrafish embryos revealed that coumarin and warfarin show teratogenic but at high doses they demonstrate lethal effects. Current researches done on humans revealed that coumarin at dose 0.1 mg/kg is tolerable and exceeded dose exhibits toxic effects. Of true, In Germany, during Christmas (consumption of cassia cinnamon) was concluded that high dose of coumarins demonstrates increased the risk for hepatotoxicity and carcinogenicity [16]. Hepatotoxicity in rats and dogs was developed after treating with 2500ppm for the 90 days of exposure [17].

Table 2. Coumarin metabolites and their toxicity

Metabolites	Study Model	Mode of action	Toxic effect	References
3,4-coumarinepoxide, o-hydroxy-phenylacetaldehyde	Mice, Rat,	conjugated with gluatathione	Hepatotoxicity	[18]
3,4-epoxidation pathway	Mice, Rat	metabolism-mediated	Mutagenic, Carcinogenicity-hepatic & pulmonary toxicity	[19]
7-hydroxylation pathway	Human	metabolism-mediated	Mutagenic, Carcinogenicity	[19]
3,7-hydroxycoumarin, o-hydroxy-phenylacetic acid	Rat	coumarin potentiation by CYP450-dependent factors	Toxic to hepatocytes	[20]
7-hydroxycoumarin, 4-hydroxycoumarin, OHPAA & o-coumaric acid	Human, rat, rabbit, mice	Presence of cytochrome P450-dependent enzymes	Toxic to hepatocytes	[21]
7-hydroxycoumarin and o-HPA	Rat, mice	CYP1A1, CYP1A2, CYP2B6, CYP2E1, and CYP3A4 pathway	Olfactory toxicity	[22]

Pharmacological properties of Coumarins

Coumarins refined from natural origins have been studied for diverse pharmacological effects like hypoglycaemic, antioxidant, antifungal, and anti-inflammatory potentials. Calanolides was isolated coumarin from the Calophyllum genus and confirmed for its potent anti-HIV effect [23].

Antidiabetic activity

As there is a reasonable relationship b/w DM and CVS problems and in such manner, the coumarins might be significantly more important on the off chance that they were viewed as

compelling against diabetes. In principle, these medications would bring down blood glucose as well as work on the results as far as the cardiovascular difficulties of diabetic patients. In such manner, various investigations have observed plant removes coumarins to display hypoglycaemic movement. Osthole consisting unpredictable oil from underlying foundations of *P. pabularia* fundamentally repressed protein tyrosine phosphatase-1B [23].

Anti-inflammatory effect

In-Vivo, carrageenan-actuated rat paw oedema was used as screening parameter. Sculetin is detached from *C. intybus*. It displayed calming action in rodent colitis initiated by tri-nitro benzene sulfonic corrosive. Esculetin stops the COX and LOX enzymes, additionally of the neutrophil-subordinate superoxide anion formation [24].

Antioxidant activity

Coumarin consists heterocyclic atoms that are related with gainful impacts on human wellbeing, like diminishing the danger of malignant growth, diabetes, cardiovascular and cerebrum infections. These impacts are believed to be connected with the extremist rummaging impact, because of their cell reinforcement exercises [25].

In Alzheimer's disease

Blocking of Acetylcholinesterase enzyme is a significant objective (pillar drug) to the administration of Alzheimer disease. Coumarin is one of the phytochemicals that is widely utilized in organic exercises such as Acetylcholinesterase blockage. The researchers have endeavoured to investigate the coumarin layout for developing newl AChE blockers with additional pharmacological exercises remembering decline for beta-amyloid affidavit and blocking od beta-secretase that are likewise significant in cure of Alzheimer's disease [26].

Anti-bacterial activity

Coumarin (45 analogues) demonstrated antibacterial potential when observed in strains of *B. cereus, E. coli, P. aeruginosa, and S. aureus*. This activity was confirmed due to their configurational modifications. Coumarin analogue- Osthenol represented the antibacterial activity with highest affinity against Gram-positive bacteria with minimum effective concentration ranging 125-62.5µg/ml. These outcomes confirmed that phenyl chain of 44 (at 8^{th} position) and the presence of OH group at 7^{th} position (of benzenic ring) are mandatory for the antibacterial effect [27].

Anti-cancer

Cancer can attack or spread to practically all pieces of the body. The expanding morbidity and high mortality of malignant growth create an extraordinary interest for the advancement of novel anticancer medications. Coumarin derivatives are universal in nature and can promptly associate with different enzymes and receptors in malignant growth cells through feeble bond collaborations; henceforth, coumarin is a profoundly advantaged pharmacophore for the improvement of novel anticancer specialists [28].

Anti-viral activity

Coumarin is one of the such natural compounds that has numerous properties like stability, solubility, and high safety margin. There are a number of evidences proving its anti-viral role to counter infection developed by viruses i. e.

Human Immuno-deficiency virus, Influenza, Enterovirus & coxsackie virus. The action refers either occupying of proteins required for viral invade, replication and maintaining of metabolic processes i. e. mammalian target ofrapamycin, anti-oxidative pathway (nuclear factor erythroid-2). It summarizes that coumarin is anti-viral and effective in cure of diseases developed by Human Immuno-deficiency virus, Hepatitis, Influenza, Dengue and Chikungunya [29].

Anti-tuberculosis

The anti-tubercular action of coumarin (natural, synthetic) was tested using resazurin microtitre test plate. Cytotoxicity of naturally obtained as well as synthetic moieties have evaluated using J 774A. The compound 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide was used to stain macrophage with minimum effective concentration, ranging from 15.6 -62.5 g/ml. The different analogues were reported for being more active to counter M. tuberculosis and multidrug-resistant bacteria. These findings confirm, coumarin analogues are more active against multidrug-resistant pathogens, and making them prone moieties in cure of TB [30].

Anti-convulsant

The anticonvulsant activity of certain modified coumarinylthiazolines, coumarinylthiazolidin-4-ones, and chromeno-thiazoles was investigated. Coumarin analogues were tested for their anti-seizure potential caused by pentylenetetrazole & strychnine. The different coumarin analogues were observed as potent anti-convulsant in PTZ-induced seizures. Compound 7b had anticonvulsant action at dose of 200 whereas phenobarbital had anticonvulsant potential (30 mg/kg) [31].

Antihypertensive activity

The mean systolic pressure and mean heart rate of coumarin- auraptene (2, 4, 8, and 16 mg/kg) was tested using tail cuff method in rats. Long-term administration of auraptene (2, 4, 8, and 16 mg/kg) lowered the BP and HR in salt-treated rodents in ascending dose manner. At the end of the 4th-8th weeks, auraptene (16 mg/kg) resulted in 7.00 percent, 10.78 percent, 16.07 percent, 21.28 percent, and 27.54 percent decreases in MSBP (P0.001). In hypertensive rats, auraptene significantly lowered MSBP, but not in normal BP (normal saline treated) animals [32].

Signalling pathways in pharmacological activities

Signalling pathway (s)	Pharmacological effect	Reference
Protecting pancreatic beta cells from injury, correcting aberrant insulin signalling Lowering oxidative damage or inflammation, activating activated protein kinase	Anti-diabetic	[33]
CYP51 Enzyme inhibition	Anti-fungal	[34]

Covalent labelling of HadA	Anti-tubercular	[35]
Carbonic Anhydrase Inhibition	Anticonvulsant	[36]
Diminishing of tumor-multidrug resistance, Microtubule polymerization inhibition	Anti-cancer	[37]
HIV-1, Reverse Transcriptase (RT) inhibition Protease Inhibition DNA Polymerase inhibition	Anti-viral	[38]

Enzyme Mimicking complexes

In 2021, Sezgin and colleagues used two complexes comprising copper (II) and manganese (II) as catecholase-like or phenoxazinone synthase mimetics under aerobic conditions: [Cu(PYC)2(H2O)2] 52 and [Mn(PYC)2(H2O)2] 53. The copper (II) complex was shown to be more effective than the manganese (II) complex, and both complexes have stronger catecholase-like activity than the phenoxazinone synthase mimic characteristics. These findings suggest that complexes 52 and 53 are a suitable place to start when developing tools for catecholase- and phenoxazinone synthase-like activities [41].

Enzyme inhibitory complexes

The inhibitory potency of palladium (II) and platinum (II) complexes of the coumarin-based ligand - 3-2-[(3-(tert-butyl)-2-hydroxybenzylidene)amino] was demonstrated by Sahin et al. 2020 [42]. acetylcholinesterase (AChE), butyrylcholinesterase (BChE), and pancreatic cholesterol esterase (cease) with thiazol-4-yl-2H-chromen-2-one 54 and 55.

CONCLUSION

The researchers have done structural modifications and developed very beneficial moieties to human kind. This demonstrated structure activity relationship (SAR) and related biochemical properties. Coumarins also reviewed for their metabolites, models used and toxic effects. All the derivatives have found an excellent scientific value as they demonstrated for their various pharmacological potentials including anti-diabetic, anti-Alzheimer's disease, antifungal, anti-tuberculosis, antiviral etc. Wang and collaborators synthesized numerous bifunctional platinum complexes (1-4) with 7-hydroxycoumarin moieties in 2019 and tested them for anticancer efficacy [39]. Complex 3 showed promising results, inhibiting COX-2 from 20.1-65.8 percent at ascending dose. Complex 3 decreases tumor-associated inflammation by releasing the right coumaric acid derivative [40]. Furthermore, recent breakthroughs in the production of metal complexes with coumarin-based ligands have resulted in probes or sensors that can detect a variety of biological analytes under physiological settings. The development of coumarin-based copper (II), iridium (III), or europium (III) complexes as fluorescence probes or PEC sensors for bioanalysis has piqued interest [43].

In Conclusion, coumarins are so effective pharmacologically and therapeutically in

terms of various healing properties including cancer, Alzheimer, Parkinson etc. In order to subside their toxicity, researchers need to modify structural configuration to enhance potential. Coumarins have been researched for possessing various novel properties as discussed above and may promising ones.

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Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

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CONFLICT OF INTEREST

Authors have declared for none conflict of interest.

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