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An Overview on Structural Modifications and Bioactivities of Coumarins

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Abstract :
The broad pharmacological spectrum and role of substituents on the bioactivities of Coumarins and exploring them as potential therapeutic agents is the field of prime interest for today's phytochemists. Since Coumarins are naturally abundant and exhibit a wide range of bioactivities, the relationship between substituents on coumarin skeleton and bioactivities helped to design the new molecules for target therapy of many chronic diseases.
Index Terms - Bioactivities, Anti coagulants, Poly hydroxy compounds , Secondary metabolites

I. INTRODUCTION

Phytochemicals are a special class of chemicals occurring naturally in the plant kingdom and have remarkable biological significance but do not belong to the category of essential nutrients, for example Flavonoids, Coumarins or Chromones and Carotenoids. Nowadays these have become an attractive field of study due to their potency against several diseases such as cancer, dementia, coronary arteries diseases and metabolic or degenerative diseases. These also show their potency as ant hyperglycemic ,neuroprotective, anticonvasculant and antiadipogenicetc.

Coumarins are a family of plant- derived secondary metabolites produced via the phenylpropanoid pathway[1]serving as a rich source of metabolites in plants, being required as a precursor for the biosynthesis of many plant derived compounds such as Flavonoids,Coumarins and Ligans. These are 2H – chromen – 2 – one and can be described as a benzene molecule with two adjacent hydrogen atoms replaced by a lactone- like chain-(CH) = (CH) – (C = O) - O - forming a second six membered heterocycle that shares two carbons with the benzene ring (Structure 1). During the past two decades Coumarins have also emerged as iron mobilizing compounds[2].

Coumarins are a family of benzopyrones(1,2–benzopyronesor2H-1-benzopyran-2-ones) widely distributed in the nature. Coumarins also known as 2H- Chromen -2- one are naturally occurring heterocyclic aromatic compounds with molecular formula$C_9H_6O_2$ and Oxygen as hetero atom. Coumarins are abundant in nature and approximately 1300 different Coumarins have been identified in nature [1].

Coumarins are phenolic substances and exhibit remarkable anti thrombotic , anti-inflammatory and vasodilatory activities. There are Coumarins as perfumes, cosmetics and industrial additives. Some of the derivatives are used as aroma enhancers in tobaccos and certain alcoholic drinks, but their most relevant role is described in natural products,organic chemistry and medicinal chemistry. Many derivatives and different salts of Coumarins are used as anticoagulants , blood thinners and are used to prevent patients suffering with atrial fibrillation, valvular heart disease or having artificial heart valves, from strokes [3] . Natural Coumarins exhibit a wide spectrum of pharmacological activities including anticoagulant, Alzheimer's disease inhibition, antibacterial, casein kinase- 2 (CK2) inhibition (Figure 1),neuroprotective, phytoalexins,antiulcerogenic and antihypertensive properties.

Coumarins are also identified as a potential nucleus for anti inflammatory molecules(Figure 2). The bioavailability of natural Coumarins along with their pharmaceutical complexity and underlying molecular mechanisms have been reviewed by a group of pharmacologists to explore the behaviour of Coumarins as secondary metabolites [4,5] . Recently Fakri Mustafa etal. [6] tried to study chemical manipulation of two coumarin based products in the seeds of two apple phenotypes and reported the trapping capacity of the natural and semi synthetic derivatives and correlated with a number of phenolic hydroxyl groups linked to the aromatic component of the coumarin backbone . The capability of the substituents ortho to the hydroxyl group to grant electron and significant decline in anti radical activity in semi synthetic derivatives have been reported[7].

II. OCCURRENCE

Coumarins are naturally abundant Phytochemicals and are found in high concentration in many plants like Tonka beans, Liquora , Cassia Cinnamon, some Cherry blossoms, Strawberries and Apricots.

III. BASIC CLASSIFICATION

Coumarins are basically classified into three classes

3.1 Simple Coumarins (Structure A)

These are wide spread natural compounds in plants with more than 700 structures described. These are well known for their vanilla -like pleasant odour. The physio chemical and therapeutic ability of these Coumarins depend upon the pattern of substitution.

3.2 Pyrano Coumarins or Benzopyrones (Structure B)

These are called 1,2- benzopyrones or 2H-1-benzopyran-2- one and are widely distributed in nature bearing a typical benzopyrone frame work.

3.3 Furo Coumarins (Structure C)

These are plant derived phytochemicals used as a natural chemical defence against predators like fungi, bacteria and insects. Furo coumarins are also found in essential oils of citrus families.

IV. CLASSIFICATION OF DERIVED COUMARINS

Apart from naturally occurring Coumarins , derived Coumarins classified as follows.

4.1 Simple Coumarins

eg. Coumarins,Esculetin, Ammoresinol, Ostruthin, Osthole, Novobiocin etc.

4.2 Furo Coumarins

eg. Imperotorin, Psoralen, Bergapten, Methoxsalen, Marmelosin etc.

4.3 Di hydro furo coumarins

eg. Anthogenol, Felahmidin, Rutaretin, etc.

4.4 Pyrano Coumarins

It is of two types

4.4.1 Linear

eg. Grandivittin, Agasyllin, Xanthyletin and Aegelinolbenzoate etc.

4.4.2 Angular

eg. Inophyllum(A,B,C,E),P,G1,G2, Calanolide A,B and F, DihydrocalanolideA and B etc.

4.5 Phenyl Coumarins

eg. Isodispar B, Dispardiol B, Mammea A/AB Cyclo E, MammeaC/ABcycloD,Disparinol D,DisparpropylinolB etc.

4.6 Bis coumarin

eg. Dicoumarol

V. STRUCTURE AND BIOLOGICAL ACTIVITY

The pharmacological benefits and over a wide range of bioactivities of Coumarins attracted the interests of phyto chemists to explore their structures and its correlation with the bioactivities' group of phytochemists introduced Coumarin based customized drugs and their structure- activity relationship targeting the side effects by virtue of structural modification [8]. It has been found that the ortho –phenolic hydroxyl group in the benzene ring has remarkable antioxidant and antitumor activities [9]. An aryl group at C -3 or C-4 position shows remarkable medicinal properties such as anti HIV, anti inflammation or anti oxidant effects . Numerous structure- activity studies suggested that the modification in the core structures develops specific sites with enhanced biological activities due to electronic or steric effects of the substituent [10] . The anti coagulant activity of the Coumarins have been reported [11] and suggested that Coumarins being Vitamin K antagonists generate anticoagulant effects by interfering with cyclic inter conversion of Vitamin K and its 2,3epoxide(vitamin K epoxide)[10]Figure 2.It has also been found that Vitamin K conversion cycle inhibition enhances anticoagulant effect of Coumarins. Esculetin is a hydroxy coumarin that is umbelliferonez in which the hydrogen at position 6 is substituted by a hydroxy group. It is used in filters for absorption of UV light. It has a role as an antioxidant, an UV filter and a plant metabolite..

VI . ISOLATION AND ANALYSIS

The methods involved are Paper Chromatography, Thin Layer chromatography Gas Chromatography, High Performance Liquid Chromatography, Titrimetric and Spectro photometric (Colorimetric and Polar graphic)methods. The physiochemical and therapeutic properties of Coumarins depend upon the pattern of substitution. The unique and versatile Oxygen containing heterocyclic structure provides electron rich and charge transport properties which is important in the interaction of this scaffold with molecules and ions. A schematic representation of molecular mechanisms and signalling pathways of the most representative and their derivatives has shown in Figure 1[12].

VII. BIOLOGICAL ACTIVITIES AND MEDICINAL PROPERTIES OF COUMARINS AND ITS DERIVATIVES

7.1 Hydroxy Coumarins

Hydroxy Coumarins have shown remarkable bioactivities. The hydroxy Coumarins are typical phenolic compounds and, therefore act as potent metal chelators and free radical scavengers. This class of Coumarins are found to be powerful chain – breaking antioxidants and display a remarkable array of biochemical and pharmacological actions (Figure 3).

7.2 Synthetic Calanolides

These are substances having poly hydroxy -poly pyranoid structures (Structure D). (+) Calanolide A (+follo10R,11S,12S]-10,11-trans-dihydro- 12- hydroxy-6,6,10,11- tetramethyl-4-propyl- 2H,6H- benzo [1,2-b:3,4-b': 5,6-b"] tripyran-2-one (+) Calanolide [13–15] and several other HIV- integrase inhibitors have a common skeleton in which two aryl units are separated by a central linker. (+) Calanolide A is an organic compound coumarin derivative having an -OH at position-12,-CH_3 at positions 6,6,10 and 11and a propyl chain at position 4.

7.3 Antibacterial

The Coumarins substituted at C-3 by ethylene moiety with substituent's like carboxylic , tertiary amines , carbonyl group, benzoyl or hydroxamate groups show effective antibacterial activity. Similarly substituent's like CH_3 or hydrogen- substituted iodinated aryloxy methyl group at C-4 and NO_2 group at C-5 of basic skeleton enhance their effectiveness as antibacterial.

7.4 Antiviral

Basic skeleton of Coumarins possesses planarity and methyl substituent at C- 3 were found to exhibit potential bio activation [19] .Presence of D- ribofuranose group at C- 3 enhances antiviral activity.

7.5 Anticoagulants

Coumarins in various substituted forms are the most widely used oral anticoagulants . Their ability to suppress formation of functional factors responsible for blood coagulation in the liver decides their potency. Their potency as oral anticoagulants is mainly during in vivo as they function by suppression of synthesis of prothrombin, proconvertin and are commonly called Vitamin K antagonists. Dicoumarol was the first of the oral anticoagulants to be isolated and used clinically. It is a 4- hydroxy coumarin derived anticoagulant used for the treatment of thromboembolic conditions.

VIII . DISCUSSION

Kostova et al [16] studied a number of such Coumarins and explored the structure activity correlation ship. According to their study various Coumarins covalentally linked to the 5' end of various oligonucleotides(OGNs) interact with HIV- 1RT differently depending upon the structure of the oligonucleotide derivatives and it was attributed to the hormone derivatives in conjugation to the OGNs which enhance the interaction with RT [17] .There are considerable evidences that Coumarins are important lead compounds for the development of antiviral and/or crucial drugs against HIV. Many synthetic Calanolides with bactericidal activity against replicating and non – replicating Mycobacterium tuberculosis have been reported [18].

Rivero et al. focused their study on the recognition of key structural features of Coumarins family to design the new analogues by studying the effects of different substituents on biological activities [24]. 4 – Hydroxy coumarins inhibit Vitamin K epoxide reductase(VKORC 1) by binding the active site leading to deficiency of Vitamin K dependent properties particularly those involved in thrombus formation [25] (Figure 4) . The Amino coumarin antibiotics Novobiocin and Chlorobiocin show potent activity against gram positive bacteria. Focusing on the structure-activity relationship studies it was found that removal of the nonbiose moiety on Novobiocin together with the introduction of a tosyl group at C - 4 or C -7 of the Coumarins provides novel lead structures exhibiting 1000 fold increased activity and enhanced rate of cell death and designed to target for cancer treatment[26–27].

The diverse biological activities of 1- azacoumarins and 6- functionalized-1- azocoumarins are undergoing human clinical trials as an oral antitumor drug. The potency of several synthetic Coumarins with a variety of pharmacophoric groups at C - 3, C – 4 and C-7 positions have been reported [28] . Coumarin –3 – sulfonamides and carboxamides exhibit selective cytotoxicity against mammalian cancer cell lines. The presence of aryloxy methyl, aryl amino methyl and di chloro acetamido methyl at C – 4 of Coumarins shows potential antimicrobial and anti inflammatory activity [28].The enhanced antioxidant and antitumor activities with ortho – phenolic hydroxyl on the benzene ring

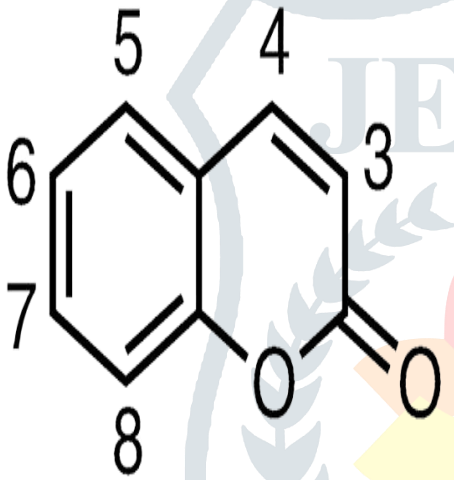
remarkable anti HIV, antitumor, anti inflammatory and anti analgesic activities of Coumarins with aryl group at C – 4 position has been reported. Phenyl at C – 3 show strong anti HIV and anti oxidant effects[8,29].

IX. TOXICITY OF COUMARINS

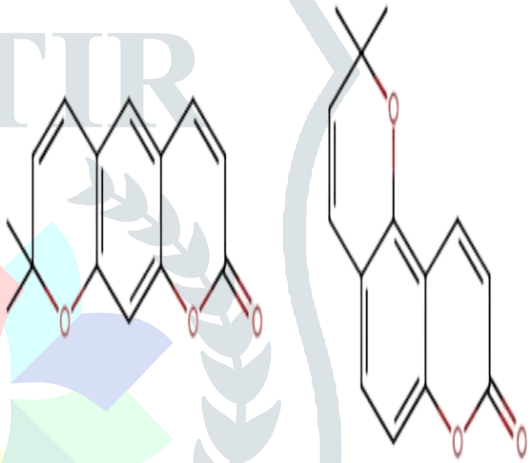
Due to the natural availability of Coumarins in vegetables, fruits, seeds, nuts, coffee, tea and wine their dietary exposure is quite high . Various studies on the biological ,pharmacological and toxicological properties of Coumarins showed some significant toxic results also. Metabolism, toxicity and carcinogenicity studies of Coumarins present in foodstuffs, cosmetics, fragrants etc. were carried out by various groups of scientists and some suggested that exposure to Coumarins from foods or cosmetic products have no health risks to humans where as some reported hepatotoxic effects and cytotoxic effects of Coumarins [20–23].

X. CONCLUSION

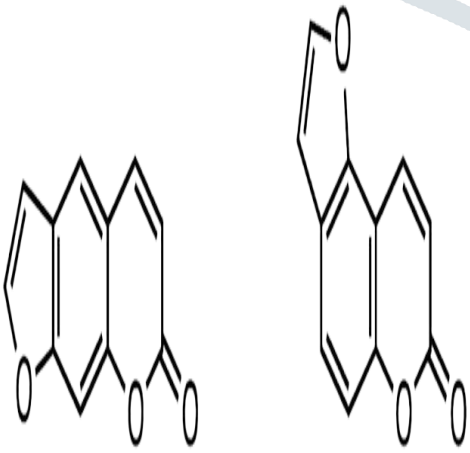
Coumarins and its several derivatives show remarkable potency towards targeted therapy and based on several pharmacovigilance data of these are found an essential element of diet due to their easy availability, low toxicity against normal cells as a potential chemotherapeutic agents. The recognition of key structural features and their effects on bioactivities of Coumarins are the field of high interest. It opens the pathways for the development of new analogues with improved activities and characterization of their mechanism of action. Various reports on the study of structural modification with substituent's proved that the specific site on the core structures of Coumarins are directly related with the electronic or steric effects on the substituents. Thus structural modification and bioactivities of Coumarins make it an effective and interesting field to explore.



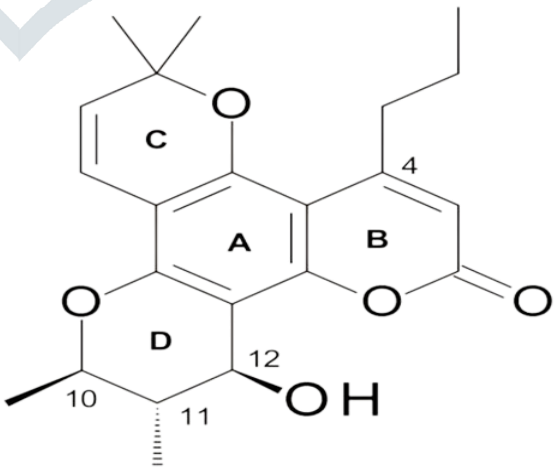
Structure A



Structure B



Structure C



Structure D

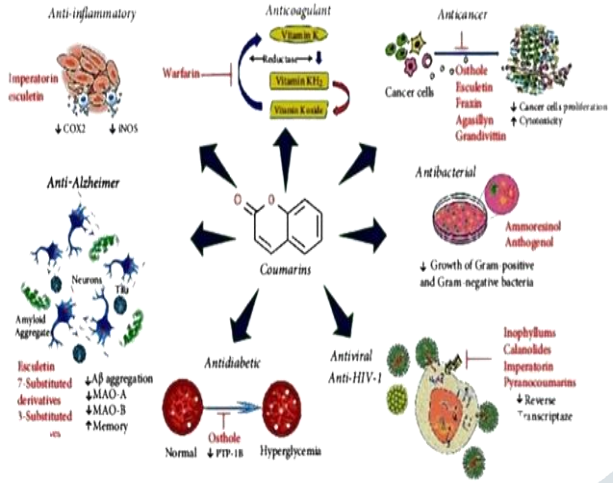
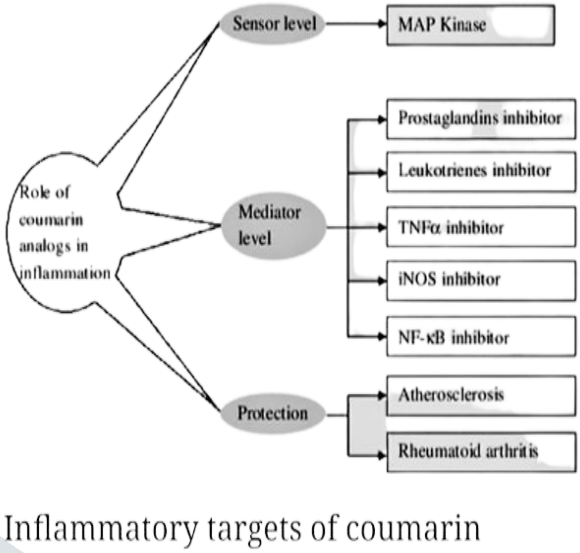


FIGURE 1



Inflammatory targets of coumarin

FIGURE 2

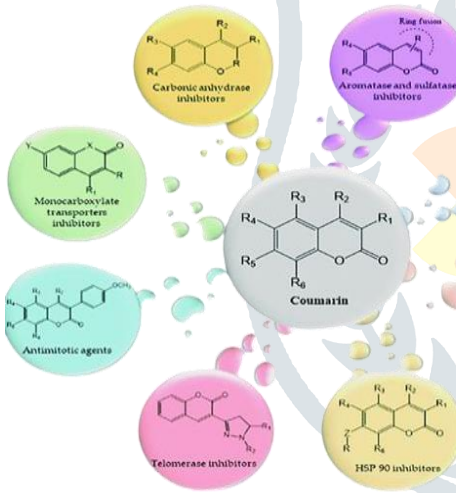


FIGURE 3

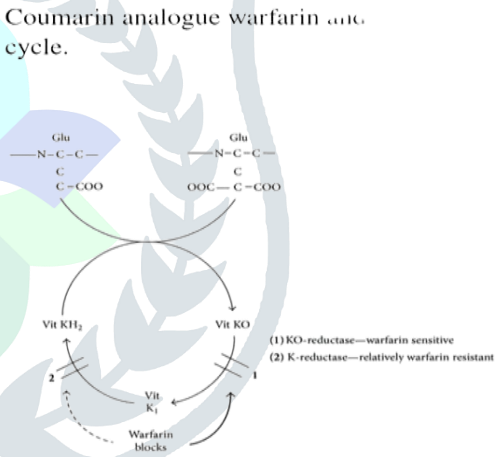


FIGURE 4

R,R1,R2,R3,R4,R5,R6 = O,OH, Other substituent.

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