Coumarin and Its Derivatives: Harnessing Nature's Compound for Modern Medicine

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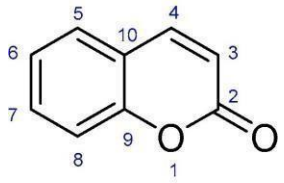
ABSTRACT
Coumarin, a compound naturally present in many plants, has garnered substantial interest in the field of medicinal chemistry and drug development due to its broad pharmacological benefits. This article provides a summary of coumarin's chemical composition, natural sources, methods of synthesis, and its wide array of biological functions and possible therapeutic uses. Notably, coumarin demonstrates properties such as antioxidant, anti-inflammatory, antimicrobial, anticancer, anticoagulant, and neuroprotection. Additionally, modifications to coumarin have led to the creation of derivatives with improved pharmacological advantages and minimized toxicity. Despite its attractive pharmacological attributes, coumarin's use is limited by potential liver toxicity at elevated doses. Research is actively ongoing to harness coumarin and its derivatives for therapeutic purposes, both as independent treatments and in synergy with current medications. This review highlights coumarin's critical role in pharmacology and its promise as a foundation for developing new treatment options for various health conditions.

KEYWORDS Coumarin structure, antidiabetic, derivatives, anticoagulant properties, pharmacology, metabolism.

INTRODUCTION: -
A broad category of secondary metabolites termed coumarins is present in many different plant species, Natural sources including microorganisms, fungi, and microorganisms, are the primary sources of identification.[1-3] The primary route for this production involves the metabolism of phenylalanine, cinnamic acid, and shikimic acid.[4-5] These natural compounds have a 200-year history.[6] Coumarin is present in significant amounts in some cinnamon varieties, making it a common way humans are exposed to this compound.

Yet, the precise extent of human exposure to coumarin remains unclear, as systematic tracking of cinnamon-containing food intake is not conducted.[7-9] The use of pure coumarin in food products is prohibited due to its potential hepatotoxic effects when consumed in large quantities.[10]Natural coumarins, of which there are over 1800 different types, are mostly found in plants, but they have also been found in microorganisms.[11] Some important microbial coumarins include novobiocin and coumermycin from Streptomyces, and aflatoxins from Aspergillus species. [12]. It has also been confirmed that some essential oils used as flavoring substances, such as Chinese cinnamon oil, cinnamon bark oil, and lavender oil, contain coumarin derivatives. [13-14]



coumarin

Fig 1: Strucuture of Coumarin Nucleus

1.1 Diverse Pharmacological Activity: - Coumarin is effective in a number of pharmacological processes including, anticoagulant [16-21], antiviral [22-26], antifungal [27- 31], and antihypertensive [32-36], Anti-inflammatory activity [37-39], anti-cancer [40-43], hypoglycemic activity [44-45], anti-diabetic [46-48], antioxidant activity[49], anti-coagulant activity [50].

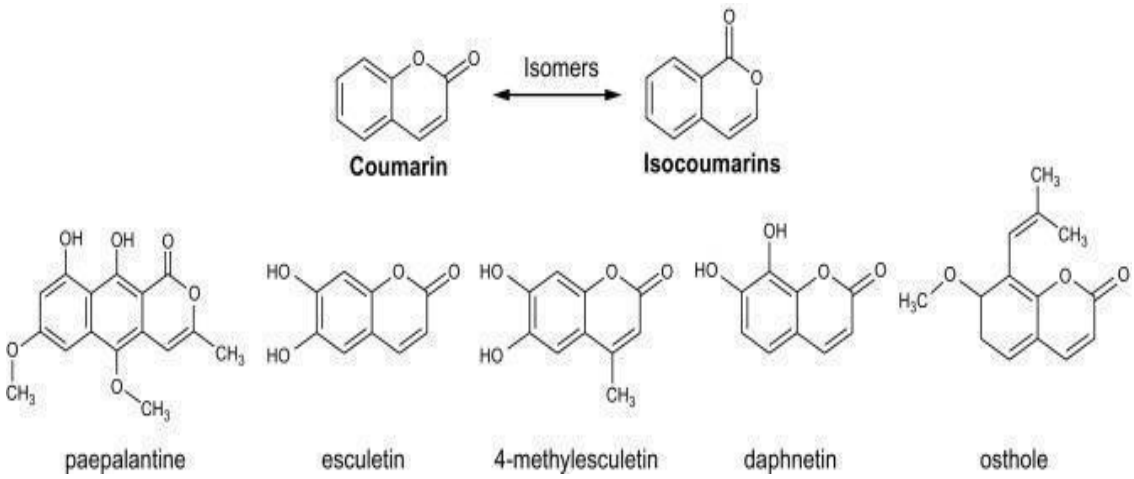


Fig 2. Coumarin containing drugs

1.2 Chemical Profile:- Coumarin is a chemical compound that has the molecular formula C9H6O2. it is identified as 2H-chromen-2-one. [51, 52] The molecule of coumarin can be represented as a benzene molecule with a, carboxylic esters, replacing two neighboring hydrogen atoms of the benzene ring.[53]

Coumarin appears as a colorless crystalline substance or powder, emitting a vanilla-like scent, and possesses a bitter, aromatic, and sharp taste.

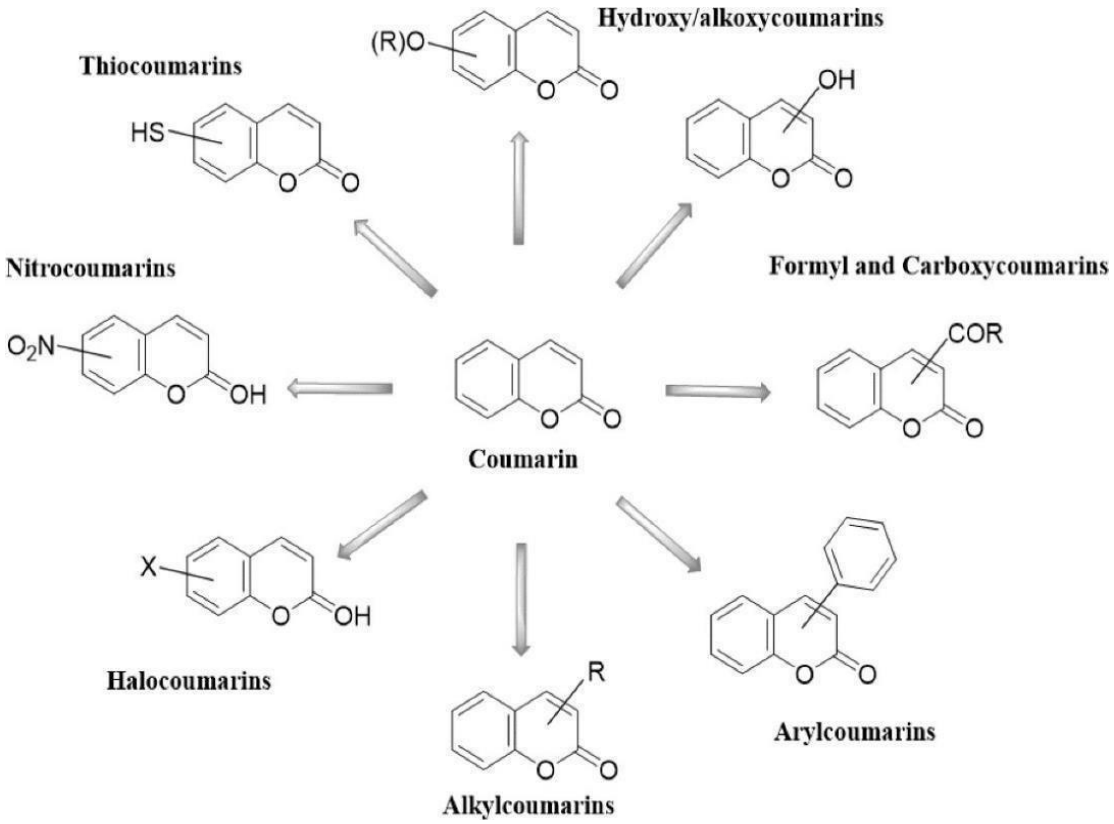


Fig 3. Natural Coumarins

Natural Coumarins: - Over the past few decades, coumarins, a naturally occurring molecule, have been the subject of much phytochemical and pharmacological research.[54-55] It is demonstrated that more than 400 coumarins have been described in scholarly journals over the past three years [56].

Coumarouna odorata, also known as the Tonka bean, belongs to the Fabaceae/Leguminosae family. contains a significant amount of these compounds . Additionally, Anthoxanthum odoratum[57] , sweet clover (genus Melilotus) , Cinnamomum cassia [58], extracts of Justicia pectoralis [59] and a significant number of cherry blossom trees contain high concentrations of it. Prangos Lindl., Ferula L., Heracleum L., Pachypleurum Hoff, Conioselinum Fisch, Libanotis L., and Seseli L. were among the Apiaceae species that have high coumarin levels.Because of its attractive asperul-like odor, coumarin was previously utilized as a foaming agent, but it is no longer in use due to its harmful effects on the liver.[60]

As opposed to this, a number of naturally occurring hydroxy coumarins are essential ingredients in a wide range of effective medications. In nature, umbelliferone is the most prevalent coumarin derivative. The umbelliferone derivatives have gained interest as potential sunburn preventives because they absorb a wide spectrum of UV light, release the energy as fluorescence, and alter the erythermal reaction to ultraviolet light. The compound umbelliferone itself has anti-Brucella malitensis and anti-Brucella abortus activity.[61]

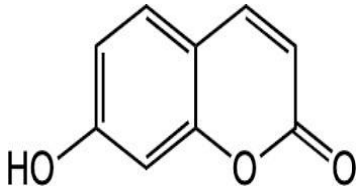


Fig 4. Umbelliferone

Toddalia asiatica contains aculeatin, a compound found in its ethanolic extract known for its antioxidative and antihyperglycemic effects. Aculeatin has been shown to reduce the expression of inflammatory genes (Mcp1, Ccl6, and Il6), increase the expression of PPAR target genes (Pparg, Ap2, Cd36, Glut4, and Adipoq), and enhance the differentiation and lipolysis of 3T3-L1 adipocytes.[62] Consequently, aculeatin could be utilized in the treatment of diabetes and dyslipidemia. Obesity and diabetes are significantly impacted by chronic inflammation. The infiltration of macrophages into adipose tissue associated with obesity and diabetes leads to the release of inflammatory cytokines such as MCP-1 and IL-6. These cytokines can inhibit IRS phosphorylation, further aggravating insulin resistance [63].

2. Clinically Active Coumarin Drugs :-

Warfarin, a medication known for its clinical effectiveness, is metabolized in the liver into inactive compounds through several hydroxylation reactions facilitated by cytochrome P450 (CYP) enzymes. The metabolism of S-warfarin, its most potent form, is primarily carried out by CYP2C9. [64]Other CYP isoforms are involved in metabolizing R-warfarin. While both CYP3A4 and CYP2C9 play roles in the metabolism of phenprocoumon, CYP2C9 is also the main enzyme responsible for metabolizing both enantiomers of acenocoumarol. Among these three coumarins, phenprocoumon has the longest elimination half-life, lasting between 110 and 130 hours. Warfarin's half-life varies, with S-warfarin between 24 to 33 hours and R-warfarin between 35 to 58 hours, making acenocoumarol's half-life the shortest of the group [65]. Due to the short half-life of S-acenocoumarol (1.8 h), acenocoumarol primarily depends on the R-enantiomer. R-acenocoumarol has an elimination half-life of 6.6 hours [66].

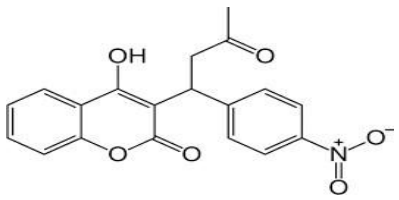


Fig 5. Acenocoumarol

Warfarin, a vitamin K antagonist, inhibits the synthesis of both anticoagulant proteins C, S, and Z and the procoagulant vitamin K-dependent factors 2, 7, 9, and 10 in the liver. These clotting factors are activated through the gamma-carboxylation of glutamic acid residues at their NH2terminal regions, a process requiring vitamin KH2, the active form of vitamin K. Vitamin KH2 is oxidized to vitamin KO, its inactive form, during gamma-carboxylation[67]. The enzyme vitamin K epoxide reductase (VKOR) then converts vitamin KO back to vitamin K,

which is subsequently reduced to vitamin KH2 by vitamin K1 reductase. This recycling of vitamin K in the liver ensures a continuous supply of vitamin KH2 for clotting factor synthesis. Warfarin disrupts this cycle by inhibiting VKOR and vitamin K1 reductase, leading to an accumulation of inactive vitamin KO and a consequent reduction in liver-produced proteins C, S, and Z, as well as vitamin K-dependent clotting factors.[68]

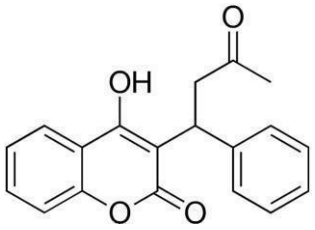


Fig 6: Chemical Structure of Warfarin

Umbelliferone, a simple derivative of coumarin, is primarily extracted and purified from Citrus aurantium and Aegle marmelos Correa. Administering umbelliferone orally at a dosage of 30 mg/kg can reduce fasting blood glucose levels and glycated hemoglobin A1c (HbA1c) in streptozotocin (STZ)-induced diabetic rats, regardless of body weight and insulin levels.[69] Research by Jarinyaporn and colleagues has shown that umbelliferone treatment significantly improves glucose tolerance in type 2 diabetic rats and mice on high-fat diets as evidenced by intraperitoneal glucose tolerance tests (IPGTT). Additionally, it has been observed that there is a reduction in liver fat accumulation, as indicated by haematoxylin and eosin staining of liver sections. The treatment also upregulates the expression of peroxisome proliferator-activated receptor (PPAR) and GLUT4 on the surface of adipose tissue. [70]

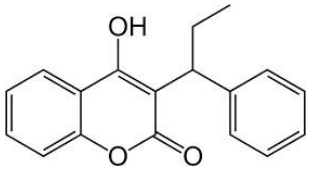


Fig. 7 Phenprocoumon

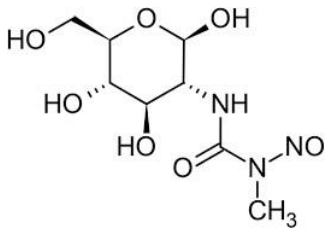


Fig 8. Derivatives of Coumarin (Streptozocin)

Umbelliferone is believed to enhance insulin sensitivity and promote the translocation of GLUT4 by activating peroxisome proliferator-activated receptors (PPAR).

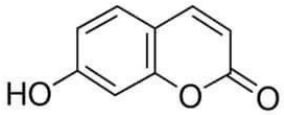


Fig 9. Chemical Structure of Umbelliferone

Oxidative stress plays a crucial role in worsening pancreatic beta-cell failure in type 1 diabetes. [72]Umbelliferone aids in combating oxidative stress by enhancing the production of antioxidants such as superoxide dismutase (SOD), glutathione (GSH), and catalase (CAT). Similarly, umbelliferone glucopyranoside exhibits the same biological activities as umbelliferone[73]. Additionally, research by Ramesh et al. demonstrated that umbelliferone reduces the levels of hydroxyproline, which in turn decreases the production of improperly folded collagen. This action is beneficial in the treatment of collagen-induced diabetic polyneuropathy and diabetic nephropathy.[74]

3. Pharmacological Activity of Coumarin Derivatives

3.1 Antidiabetic Activity

High blood sugar levels are the hallmark of diabetes, a chronic metabolic condition that is typically brought on by insufficient insulin synthesis by pancreatic cells or by a person's body's inability to utilize this hormone Diabetes can lead to severe complications, including blindness, kidney failure, heart attacks, strokes, and the amputation of lower limbs.[75] In theory, enhancing pancreatic function and mitigating diabetic outcomes can be achieved through various cellular and metabolic interventions, such as inhibiting oxidation and inflammation, boosting insulin production, augmenting insulin's effectiveness in target tissues, and diminishing the complications associated with diabetes.[76]

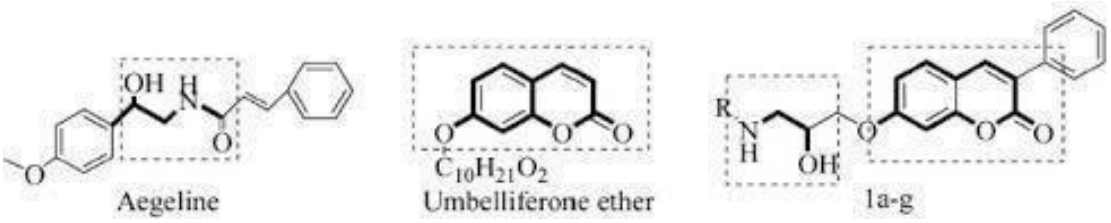


Fig 10. Antidiabetic Agents

3.1.1. SGLT 2 inhibitors:- 90% of renal glucose reabsorption in the kidney is carried out by sodium-dependent glucose co-transporter, a low affinity and high capacity glucose transporter that is primarily expressed in the kidneys. Sodium glucose co-transporter inhibitors in the proximal convoluted tubule reduce glucose reabsorption to enhance urine glucose excretion, which lowers blood glucose levels and provide beneficial therapeutic energy.[77]

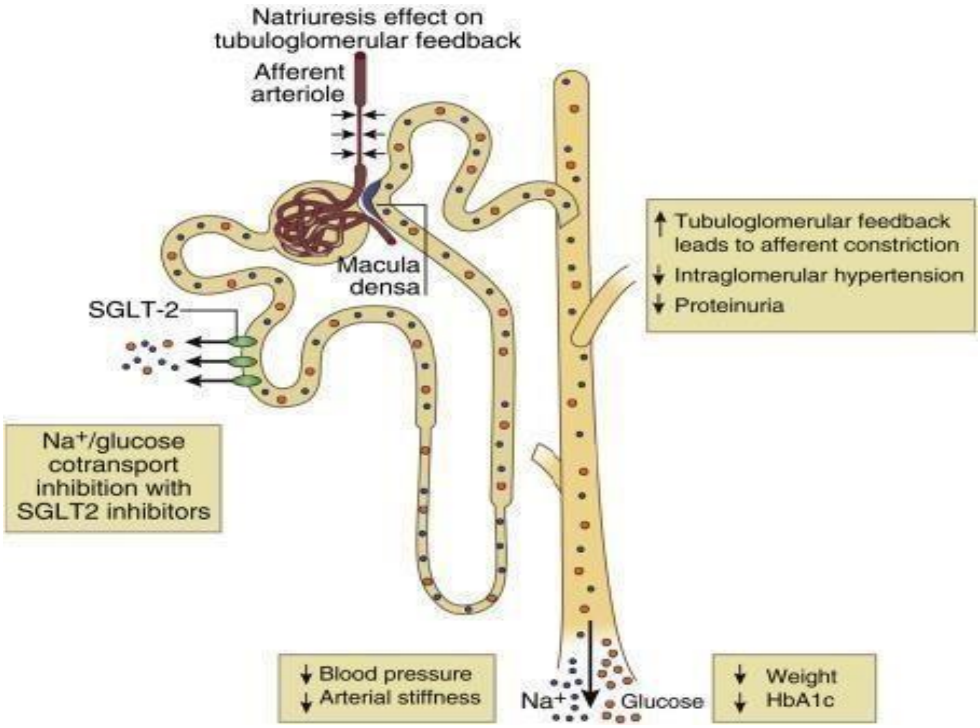


Fig 11. Sodium- dependent glucose co-transporter

3.1.2 Glucose transporter 4 (GLUT4) expression or translocation:- A crucial element in maintaining glucose homeostasis and removing glucose from the blood is GLUT4. GLUT4

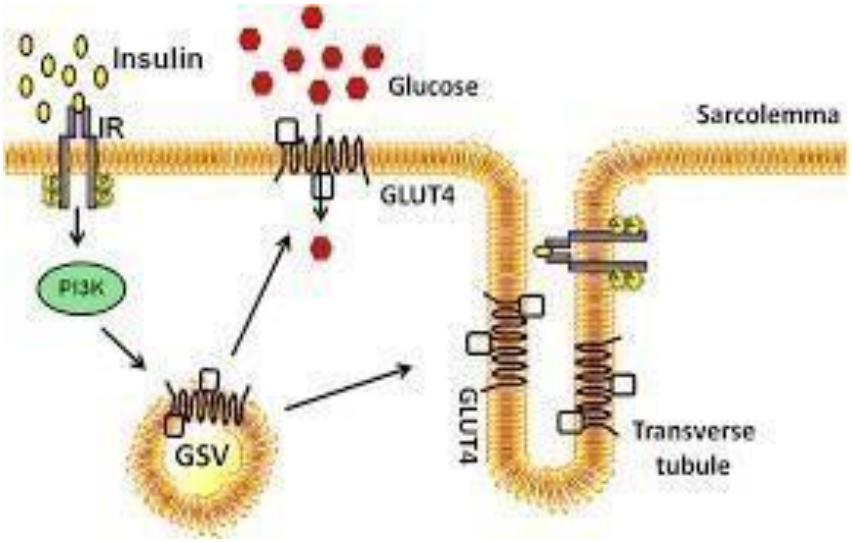
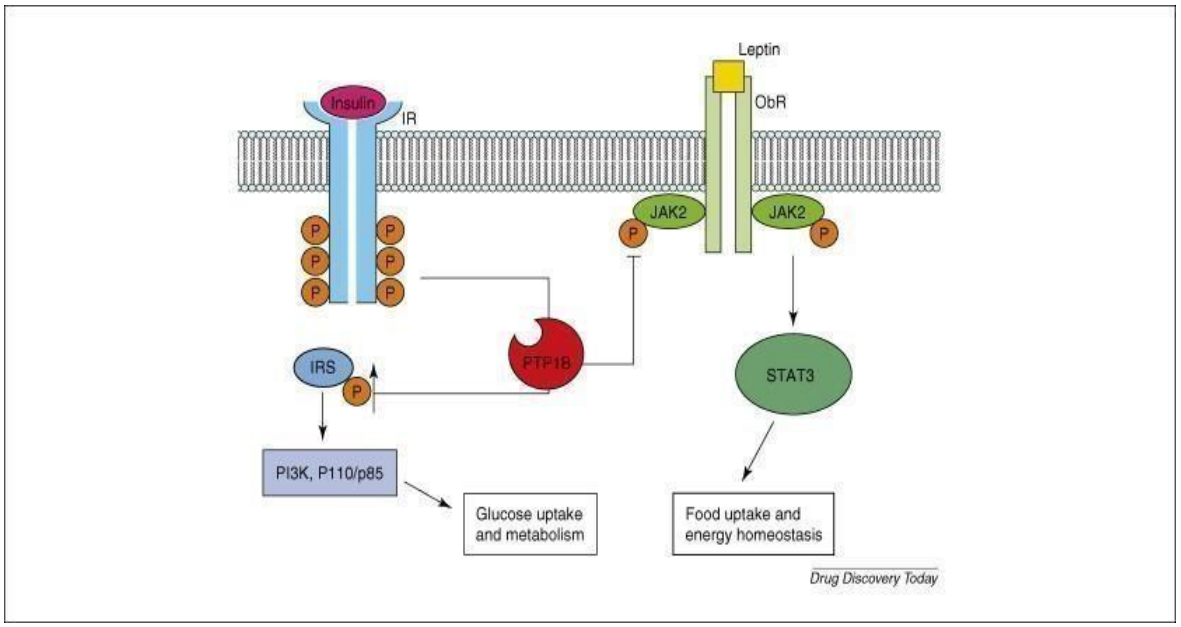


Fig 12. Glucose transporter 4 (GLUT4) expression or translocation

roles in the glucose translocation caused by insulin. Insulin promotes GLUT4 in the muscle cell to take in glucose, which is then converted to glucose-6-phosphate by hexokinase. When glucose is available, the cell can then use the glucose-6-phosphate for either glycolysis to produce energy or for the production of glycogen. Adipose tissue's increased GLUT 4 level raises the possibility that umbelliferone might improve insulin sensitivity. and stimulate PPAR-gamma to induce GLUT4 translocation.[78].



3.1.3 PTP1B inhibition:- Consequently, these molecules have become promising targets for enhancing insulin sensitivity. Protein Tyrosine Phosphatase 1B (PTP1B) can dephosphorylate proteins within the leptin signaling pathway, such as insulin receptor substrate (IRS), janus kinase (JAK), and signal transducer and activator of transcription 3 (STAT3), potentially blocking both insulin and leptin signaling pathways. In liver cell models like Fao hepatoma cells, overexpression of PTP1B disrupts insulin-stimulated glucose metabolism, while a lack of PTP1B increases insulin sensitivity in the liver. Therefore, targeting PTP1B could offer a therapeutic strategy for type 2 diabetes and obesity. [79].

3.1.4. Suppression of *α*- glucosidase :- The enzymes glucosidase or maltase, which aid in the conversion of simple monosaccharides like glucose from disaccharides, will be inhibited by coumarins.[80]

3.1.5. PPAR *γ* agonists:- PPAR-, a protein that plays a key role in controlling lipid and glucose metabolism, has been connected to the pathogenesis of metabolic diseases such obesity, diabetes, and hyperlipidemia. It acts as a target for one class of insulin-sensitizing medications knownasthiazolidinediones(TDZs) [81].

AMPK activation:- AMPK is dual-regulated by the AMP/ATP ratio and Thr172 phosphorylation on the a subunit, acting as a significant cellular energy sensor and a crucial regulator of metabolic homeostasis in response to a variety of stimuli, including cellular stress, exercise, and a wide range of hormones and agents. It is now evident, in accordance with , that AMPK is a critical target for enhancing insulin sensitivity and that it mediates some of the therapeutic benefits of metformin. This study examines a number of coumarins that work through AMPK activation. In addition to lowering glucose absorption, efficient a-glucosidase inhibitors may also lower postprandial hyperglycemia and glucose tolerance [82].

3.2 **Anti-Cancer Activity:-** Cancer is defined as a group of cells with the capability to invade or spread to other parts of the body, either by growing directly into nearby tissues or by dispersing cells to distant locations via metastasis. Identifying the precise cause of cancer in many cases is challenging. Factors increasing cancer risk involve exposure to chemicals, dietary practices, lifestyle choices, and human exposure.[83]

Research into the role of coumarins in biology has uncovered numerous ways through which they deliver their anticancer properties. These methods range from inhibiting kinases, arresting the cell cycle, preventing angiogenesis, inhibiting the heat shock protein HSP90, telomerase inhibition, antimitotic effects, blocking carbonic anhydrase, inhibiting monocarboxylate transporters, aromatase, and sulfatase. Furthermore, coumarins affect various other cancer pathways. This research has also facilitated structural activity relationship (SAR) studies, leading to the identification of several substitutions in the coumarin nucleus that have broadened and enhanced their spectrum of activity..[84]

Anti-mitotic agents:- N.H. Kim and colleagues have identified that coumarin derivatives, via pathway vi, play a significant role in halting cell division by directly influencing the mitotic stage, particularly during prometaphase and metaphase. This is the critical period when chromosomes are separated into two identical groups for each nucleus. Such activity indicates that these compounds specifically target microtubulin. In addition, they have synthesized antimitotic agents in 2013, utilizing allylpolyalkoxybenzenes derived from plants to create polyalkoxy-3(4methoxyphenyl) coumarins.[85] To assess the antimitotic effectiveness of these drugs, the researchers employed a phenotypic sea urchin embryo experiment. Findings from the StructureActivity Relationship (SAR) analysis highlighted that compound 38 exhibited a pronounced antimitotic effect, attributed to the presence of methoxy groups at the C-5, C-6, and C-7 positions. This antimitotic action is linked to tubulin targeting, which, at a concentration of 4 M, led to cleavage arrest and the formation of tuberculate eggs, both symptoms of microtubule destabilization. Furthermore, this compound was tested against 60 human cancer cell lines at the National Cancer Institute (NCI) in the United States, demonstrating its ability to inhibit cancer cell growth with an average GI50 value of 3.981 [86]

3.2.1 Monocarboxylate transporters (MCT) inhibitors:- It has been observed that coumarins can inhibit the process of lactate absorption. In conditions of low oxygen (hypoxia), cancer cells metabolize glucose at an accelerated rate, resulting in the rapid production and release of lactate. This lactate is then reabsorbed by cancer cells in oxygen-rich environments, fueling the tricarboxylic acid (TCA) cycle and promoting the rapid growth of tumors. [87]The key proteins responsible for lactate transport are identified as monocarboxylate transporters (MCTs), with MCT1 and MCT4 being particularly abundant in cancerous cells. Research conducted by N. Draoui and associates highlights that MCT1 demonstrates a stronger affinity for lactate, facilitating its uptake by oxidative tumor cells. On the other hand, MCT4, while having a lower affinity for lactate, shows a higher rate of turnover and is predominantly found in glycolytic tumor cells and tumor-associated fibroblasts, which are involved in lactate exportation..[88]

By inhibiting MCTs, coumarins obstruct the ability of oxygen-rich cancer cells to utilize lactate, thereby compelling them to depend on glucose for energy. This mechanism effectively starves hypoxic tumor cells, which rely heavily on glucose, leading to their demise due to a lack of glucose replenishment. In response to this discovery, Draoui and colleagues developed carboxycoumarins and evaluated their capability to inhibit lactate transport. Their comprehensive Structure-Activity Relationship (SAR) analysis revealed that the presence of carboxylic acid functionality is crucial for inhibitory activity, whereas substituting this group with an ester completely negates the effect. Enhancements in activity were observed with the addition of an Obenzyl or a secondary amino group at the C-7 position of carboxycoumarin. Conversely, modification of the methyl group at C-7 or replacing the lactone ring with a lactam

rendered the molecule inactive. For effective lactate transport inhibition, the presence of an oxygen atom in carboxy coumarin and an unobstructed position 4 are vital. They discovered a compound with an EC50 of 0.22 μM and an IC50 of 0.059 μM, significantly outperforming the reference compound α-Cyano-4-hydroxycinnate (CHC), which has an EC50 of 10.7 μM and an IC50 of 43.5 μM, as the most effective lactate uptake inhibitor. This compound did not exhibit any anticoagulant side effects, and its in vitro ADME study showed good aqueous solubility, addressing a common issue with many coumarin analogs, according to N. Draoui and team. [90]

Cell Cycle Arrest:- Coumarins are reported to halt various phases of the cell cycle, including G0, G1, S, and M, ultimately leading to apoptosis. This apoptotic induction is mediated by altering the levels of Bcl-2 family proteins and through a caspase-dependent intrinsic pathway. The increase in proapoptotic Bax/Bak and intracellular reactive oxygen species (ROS) significantly diminishes mitochondrial potential, triggering the release of cytochrome c from mitochondria due to the activation of initiator caspase-9 and executioner caspases-3/7, which further decreases matrix metalloproteinase, allowing entry into the cytoplasm.[91] The tumor suppressor protein p53's transcriptional target, PUMA, is upregulated, promoting the activation of Bax/Bak by interacting with antiapoptotic Bcl-2 family proteins, playing a critical role in various apoptotic pathways.[92]

Kumar et al. evaluated the antitumor properties of 3-(4, 5-dihydro-1-phenyl-5-substituted phenyl1H pyrazol3-yl)-2H-chromen-2-one derivatives against 60 cancer cell lines, identifying the coumarin nucleus's lactone ring as essential for their significant anticancer activity, primarily through G1 cell cycle arrest. Modifications to coumarin were also explored to prevent lactone hydrolysis in the bloodstream, allowing hydrolysis only within the target tissue, which halts the cell cycle. These changes also enhanced the drug's bioavailability. The most potent anticancer agent was identified as having a 4-hydroxy substitution on the phenyl ring, according to chemical structure analysis and in vitro cancer screening.[93] Musa et al. investigated the cytotoxic effects of eight acetoxycoumarins on various cancer and normal cell lines, using a crystal violet dye binding assay to evaluate cytotoxicity. [94]Compound 19 was found to exhibit cytotoxicity in the CRL 1548 liver cancer cell line with an LD50 of 45.1 μM. Compound 18 showed cell cycle arrest in A549 cells at different phases depending on the concentration, highlighting its potential as a lead for anticancer drug development, despite showing tissue-specific toxicity.[95]

SAR characteristics revealed that the cytotoxic action of coumarin was enhanced with specific substitutions at C-4, C-7, and C-2. A SAR study by Vazquez et al. on ortho-dihydroxycoumarins demonstrated specific pro-apoptotic actions, with cell cycle analysis revealing a decrease in G0/G1 phase cells and reduced clonogenic potential. Compounds with ortho-dihydroxy substitution showed the highest activity, while those with meta-dihydroxy substitution showed the least. Substituting hydroxy groups with less active groups and exploring monoamine derivatives also provided insights into activity levels.[96]

Zhang et al.'s study on 4-(1, 2, 3-triazol-1-yl) coumarin derivatives against various cancer cell lines identified a compound with significant antitumor activity, linked to G2/M phase cell cycle arrest and apoptosis induction. SAR analysis indicated that rotatable bonds and specific substitutions at C-6 and C-7 enhance receptor binding, while certain replacements can diminish antitumor activity.[97]

3.3 Anticoagulant Activity:- The body's intricate system regulates blood fluidity. When exposed to injury, blood must clot fast and remain inside the vasculature. Warfarin and vitamin K share a lot of structural similarities. Warfarin is classified as a blood anticoagulant. Due to this structural and functional similarities, warfarin is considered a vitamin K antagonist. Warfarin was initially employed as a poison to kill lab rats during trials; nevertheless, For the last six decades, it has been recognized as a blood thinner.[98]

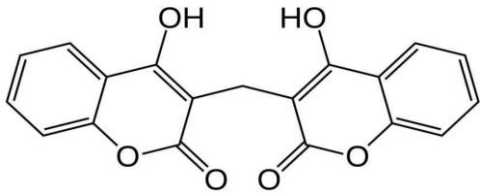


Fig. 13: Chemical Structure of Dicoumarol

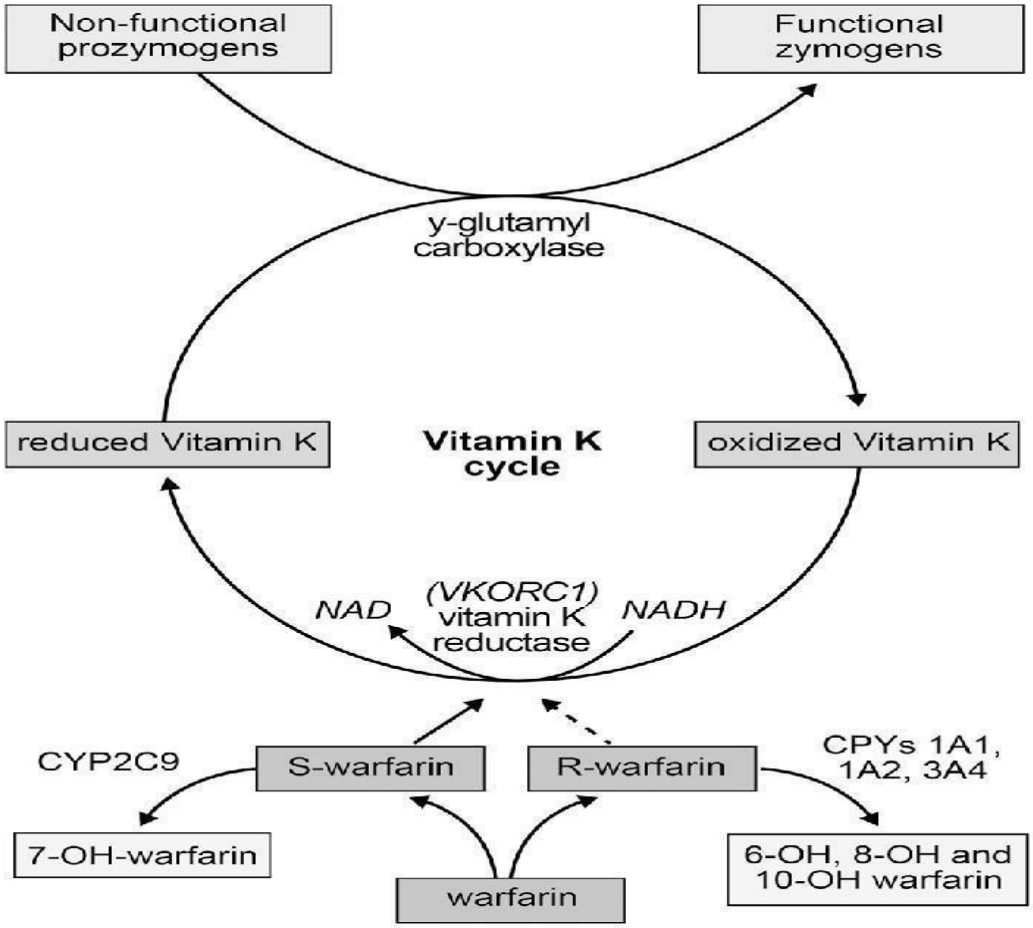


Fig. 14: Mechanism of Action of Anti-coagulant agents

3.4 **Anti Alzheimer Activity**:-

Cinnamon, tonka beans, and sweet clover are just a few of the plants that contain coumarin, a natural chemical component. While coumarin has been researched for a number of possible health advantages, it has also been linked to certain worries about liver toxicity and, to a lesser extent, its potential effects on cognitive and nervous system function. Limited scientific evidence exists directly linking coumarin with the prevention or treatment of Alzheimer's disease. Alzheimer's, a complex neurodegenerative disorder influenced by numerous factors, is commonly addressed through lifestyle modifications, genetic considerations, and diverse medical interventions. While a range of substances, including natural compounds, are under investigation for their ability to combat Alzheimer's, coumarin has not emerged as a primary or established treatment option. It's crucial to remember that

coumarin may be harmful to the liver and cause other health problems in excessive levels, which is why several nations control its usage in food and dietary supplements. It is crucial to speak with a healthcare expert for advice and to assure safety if you or someone you know is thinking about taking coumarin or any other drug to address cognitive or health difficulties. Known for its wide range of pharmacological characteristics, including possible impacts on neurodegenerative disorders like Alzheimer's disease, Coumarin, a compound found naturally in numerous plants, is under investigation for its potential role and effectiveness in Alzheimer's disease treatment. It's important to note that the impact of coumarin on Alzheimer's disease prevention, including its anti-inflammatory properties, is still being explored. The hypothesis is that brain inflammation plays a part in Alzheimer's progression, and coumarin's anti-inflammatory effects might be beneficial in reducing neuroinflammation. [99]

2. Antioxidant Activity- Coumarin has antioxidant characteristics that may aid in preventing oxidative stress on brain cells. It is believed that oxidative stress has a role in the progression of Alzheimer's disease.
3. Acetylcholinesterase Inhibition: Studies have shown that specific types of coumarin derivatives could inhibit the function of acetylcholinesterase, an enzyme that breaks down acetylcholine in the brain. Acetylcholinesterase inhibitors are commonly prescribed for Alzheimer's disease treatment, as they help in preventing cognitive decline associated with low levels of acetylcholine in the brain.
4. Anti-Amyloid Properties: The development of beta-amyloid plaques in the brain is a hallmark of Alzheimer's disease. Some studies suggest that coumarin compounds may prevent plaque formation or accelerate their removal.[100]

3.5 Anti-inflammatory Activity:- Salicylic acid, pyrazolone, and phenacetin (also known as acetophenetidin), identified in the nineteenth century, form the basis for most anti-inflammatory pain relievers. Despite their chemical differences, these compounds are effective in targeting the root of inflammation and providing relief from mild to moderate pain. [101]

Acetylsalicylic acid, better known as aspirin, emerges from salicylic acid and stands as the most commonly utilized mild pain reliever. It sets the standard for anti-inflammatory analgesics, alongside two other primary types: acetaminophen, which originates from phenacetin, and aspirin-like medications, or nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, naproxen, and fenoprofen. Pyrazolone derivatives, despite some exceptions, have largely fallen out of favor in numerous countries due to their risk of triggering a severe infection called agranulocytosis.[102]

Aspirin and NSAIDs share a similar mechanism of action, blocking the formation of prostaglandins. These substances are naturally produced by irritated white blood cells and lead to symptoms such as pain and inflammation in the affected tissues. Essentially, aspirin and all related analgesics, including those derived from the indole chemical structure like indomethacin and sulindac, inhibit prostaglandin synthesis. These drugs are categorized into nonselective and selective COX inhibitors, based on their action on the cyclooxygenase (COX) enzyme responsible for prostaglandin production. COX exists in two forms: COX-1, found in most normal tissues, and COX-2, which appears during inflammation. COX-2 selective inhibitors, such as rofecoxib and celecoxib, tend to cause fewer gastrointestinal issues than other NSAIDs, mainly because COX-2 is rarely expressed in the stomach. However, unlike aspirin and other non-selective COX inhibitors, COX-2 selective inhibitors do not impact platelet clot formation. Analgesic efficacy was assessed in substances at a 20 mg/kg body weight dosage, revealing significant pain relief with compounds featuring dichloro and o-chloro, akin to diclofenac sodium. [103]Further investigations on o-chloro phenyl compounds evaluated their potential ulcerogenic effects, identifying a particularly effective analgesic agent with 2,6-dichloro phenyl that does not cause ulcers. Gupta and colleagues explored the anti-inflammatory and analgesic capabilities of various 5-(substituted) aryl-3- compounds at 200 mg/kg, noting substantial effectiveness against chronic conditions like adjuvant-induced arthritis compared to diclofenac. These compounds also exhibited noteworthy anti-inflammatory, antipyretic, and analgesic properties with a minimal ulcerogenic risk.

The anti-inflammatory qualities of triheterocyclic thiazoles containing coumarin and carbostyril were examined, with specific substitutions on the carbostyril ring enhancing the coumarin's antiinflammatory effects. Testing on albino rats with various N-aryl compounds showed efficacy comparable to piroxicam and phosphonic acids dimethyl ester against leukemia cell lines HL-60 and NALM-6. [104]

3.6 Antifungal Activity:- Candida albicans is a fungal species commonly found as a harmless inhabitant on human skin and in the gastrointestinal tract. The rise in opportunistic fungal infections has been linked to the extensive use of broad-spectrum antifungal agents, such as azoles, polyenes, allylamines, echinocandins, and 5-fluorocytosine, necessitating the development of more effective antifungal treatments against severe candidiasis. Coumarin compounds have demonstrated inhibitory effects on various fungal infections in humans and plants, including Aspergillus fumigatus, Candida albicans, and Candida tropicalis. It's known that 24-hour exposure to coumarin can disrupt the cell wall and membrane structure of C. albicans, although the exact mechanisms remain unclear.[105]

The search for new antifungal drugs is imperative due to the limitations and adverse effects of current treatments, including resistance. Compounds like lycopene, nerol, and limonene are recognized for their potential antifungal properties through apoptosis induction, a crucial process for removing harmful or unnecessary cells, also observed in unicellular organisms like C. albicans. [106]This study has found that coumarin impedes cell growth and reduces fungal strain viability, triggering apoptosis in C. albicans through mechanisms such as phosphatidylserine externalization, DNA fragmentation, cytochrome c release, and metacaspase activation, contrary to previous findings that suggested cell death via pore formation in the cell wall and necrosis.[107] Differences in experimental results may arise from variations in C. albicans strains, culture conditions, incubation temperatures, and coumarin exposure durations. The role of reactive oxygen species (ROS) and mitochondria is pivotal in apoptosis, with oxidative stress opening the mitochondrial permeability transition pore, leading to cytochrome c release and caspase activation. [108]Coumarin exposure increases ROS levels, disrupts mitochondrial membrane potential, and alters mitochondrial shape, indicating that coumarin induces apoptosis via ROS accumulation and mitochondrial dysfunction. Furthermore, apoptosis is closely linked to calcium dynamics, with apoptotic signals often causing cytosolic calcium increases from both extracellular influx and intracellular release.

In a comprehensive evaluation, 40 coumarins were tested for antifungal efficacy against Candida albicans, Aspergillus fumigatus, and Fusarium solani using the broth microdilution method. Osthenol emerged as the most potent antifungal agent, particularly effective against Fusarium solani and also against Candida albicans and Aspergillus fumigatus, possibly due to an alkyl group at the C-8 position. [109]

3.7 Anti-Oxidant Activity :- Food antioxidants are a crucial component of health protection. Research suggests that incorporating antioxidants into one's diet could lower the chances of contracting chronic conditions, including cancer and cardiovascular diseases. Natural antioxidants are mostly found in whole grains, fruits, and vegetables. vitamin E, Vitamin C, carotenes, phytate, phenolic acids, and phytoestrogens are a few examples of the antioxidants contained in foods made from plants that are known to reduce the risk of disease. The majority of antioxidant substances that make up a regular diet come from plant sources and fall under a variety of chemical and physical substance categories. Mono-phenols, for example, only show sporadic antioxidant activity while certain substances, such as gallates, have high antioxidant activity.[110]

Coumarins and their derivatives, one of the most effective chemical classes, have a variety of biological effects. Numerous of these chemicals have been shown to be effective as bacterial, fungal, inflammatory, coagulant, HIV, and cancer medications. Optical brighteners, dispersed fluorescent and laser dyes, food, cosmetics, pharmaceuticals, and food all include coumarins as additives. Coumarins demonstrate remarkable optical features, such as broad spectrum sensitivity, outstanding quantum yields, and superior photostability, alongside exceptional thermal stability. [111]

It has been established for many years that coumarin and compounds related to coumarin have significant medicinal promise. Various natural sources produce coumarin derivatives, and new ones are regularly discovered or synthesized. Many of the derivatives of the basic chemical coumarin have been recognized for more than a century. However, their vital role in the biology

of plants and animals remains little understood. According to the research, coumarin and compounds related to coumarin constitute a rich source of potential medications.[112]

Flavonoids and coumarin, types of heterocyclic compounds, are associated with potential health advantages, including lowering the risk of several ailments like cancer, diabetes, cardiovascular diseases, and mental health issues.

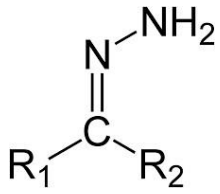


Fig 15. Hydrazones

Due to their use as drugs, fluorescence sensors, chemoreceptors, and precursors for the production of coumarin pyrazoles, coumarin derivatives, such as coumarin hydrazones, have come under investigation recently. A hydroxyl group substitution in coumarin derivatives exhibits antifungal and antibacterial properties. The addition of another heterocyclic molecule changes the characteristics of coumarin, resulting in compounds with new or intriguing features either as a substituent or a fused component.[113].

The risk of cardiovascular, brain, and neurological disorders, diabetes, cancer, and coumarins has been shown to be reduced by the heterocyclic substances known as flavonoids and coumarins. These effects are believed to be linked to their antioxidant properties and potential antiinflammatory pathways, including radical scavenging effects.

aspects and interactions with several enzymes. The importance to comprehend the chemistry underlying the antioxidant properties of both natural and synthetic compounds when taking into account both their dietary and pharmacological benefits has been indicated by a number of studies on coumarins and flavonoids that have been published in the last two decades. In this study, antioxidant flavonoid and coumarin properties in humans will be reviewed, along with structural elements.[114]

3.8 Anti-Hypertensive Activity:- The novel coumarin dihydromammea was produced by the Mammae Africana sabine tree in west Africa. The molecular structure has been revealed using the single crystal X-ray method. Studies have looked into the antihypertensive effects of stem bark extracts from mammae . The coumarin's vasodilator actions on cultured microbial cells have also been reported. Scopoletin was extracted from the fruits of Tetrapleura tetraptera TAUB, relaxes smooth muscles and lowers blood pressure in both in- vitro and in-vivo test animals. Angina pectoris has been treated using visnadine, an active ingredient produced from the fruit of Ammi visnaga, because it possesses coronary and peripheral vasodilator effects. Khellactone from Phlojodicarpus sibiricus was isolated, and its vasodilatory action pattern was noted.[115]

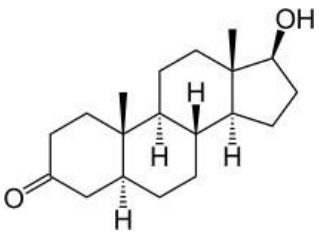
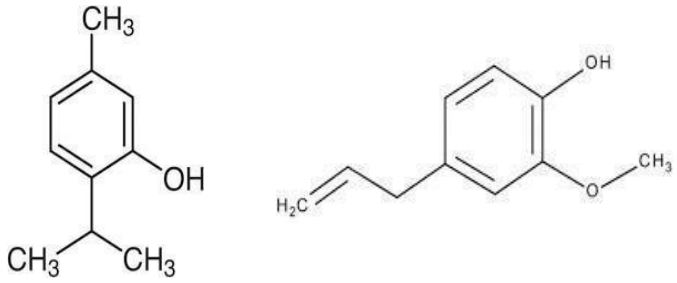


Fig 16. Dihydromammea

3.9 Anti-Bacterial Activity:-

Newer resistant bacteria continue to emerge throughout time with the introduction of any new generation of antibiotics or medications. Bacterial consortia can obtain traits from both nearby and far-off bacteria according to the inherent/intrinsic mechanisms of bacterial genetic exchange. Every year, infectious diseases claim the lives of almost 17 million people worldwide, and they also harm 50,000 people of every age group. As a result, using antibiotics causes them to quickly lose their potency, leaving a gap in the market for sought-after antibacterials. [116].

A viable approach for the creation and development of new drugs involves the molecular combination of two lead compounds showing similar biological activities. This process includes merging two different pharmacophoric groups to form a single hybrid lead molecule. Natural products such as vanillin, thymol, eugenol, menthol, umbelliferon, carvacrol, among others, are utilized for their antibacterial, antifungal, and anticancer properties through established medicinal chemistry methods. [117]. Additionally, coumarin, a type of phytochemical, can be chemically linked with a glycoside, a carbohydrate, and is naturally present as a component of benzopyrone. The term "pyrone" denotes a ring structure formed by the fusion of benzene and lactone, closely related to chromone, yet distinct in the positioning of the carbonyl or ketone group in each specific case.



Thymol Eugenol

Fig 17. New Drugs

Commercially recommended antibiotics such as "Novobiocin," "Chlorobiocin," "Aminocoumarin," among others, are derived from carboxamide coumarin. These derivatives have been reported to possess antioxidant, antimicrobial, antidiabetic, anticancer, and antiviral properties. In this study, structure-activity relationship (SAR) analyses were conducted to evaluate the synthesis strategies for coumarin derivatives and their effectiveness against various detrimental bacterial strains.[118] Additionally, by incorporating different substituents as functional groups, introducing new molecular frameworks, and forming metal ion complexes at various positions on the coumarin structure, several promising antibacterial coumarin candidates were developed. Similarly, structural modifications of norharmane, a bioactive compound found in nature, and nostocine, a phytochemical, were undertaken with the goal of discovering new anticancer agents.[119]

3.10 **Anti-Viral Activity:-** There has been some investigation into coumarin's antiviral action, while it has mostly been examined for its aromatic qualities and prospective medical use. According to certain research, coumarin derivatives may be able to fight against viruses like HIV, hepatitis C, and herpes simplex, as well as other viruses. Developed nations as a whole have been placed under quarantine, and generations who have never experienced a medical emergency are now dealing with the aftereffects of the viral spread. The recurrent emergence of pandemics throughout human history can be attributed to the ability of viruses to mutate and the continuous introduction of new viruses into the medical landscape.[120]

Nature is a priceless source of inspiration. beneficial medicinal chemicals, and various natural molecules that have antiviral activity can be used to treat viral infections. Coumarins and other polyphenolic chemicals have strong antiviral effects. The many ways by which coumarins exert their antiviral activity have an impact on the viral life cycle and their biological activities can change based on the conjugation of different substituents and conjugates. Several viruses, including chikungunya, seem to be resistant to coumarins.[121]

Liu and his team conducted a phytochemical examination of the Clausena lenis stem, uncovering three new and nine previously identified prenylated coumarins. They explored the compounds' capabilities against HIV reverse transcriptase (RT) and their anti-inflammatory effects. The evaluation involved cytotoxicity testing on the C8166 cell line (CC50) and assessing the inhibition of HIV-1's cytopathogenic activities (EC50) using MTT methods. The three newly discovered compounds exhibited superior inhibitory performance, with EC50 values of 0.29, 0.68, and 0.17 μM, respectively, without showing cytotoxic effects on the C8166 cell line (CC50 > 200.00 μM).[122]

In a 2019 study by Liu et al., interest in prenylated coumarins surged following their discovery in the fruits of the evergreen tropical tree Manilkara zapota, marking a novel finding. The research team assessed the anti-inflammatory and anti-HIV activities of three new derivatives alongside seven known ones using the aforementioned techniques. The newly identified prenylated coumarins from Manilkara zapota fruits demonstrated significant anti-HIV RT activity, with one compound notably achieving an EC50 value of 0.12 μM. The study highlighted the importance of the isopentenyl group at C6 and the 2-methylbut-3-en-2-yl group as substituents, among other coumarin derivatives extracted from the fruits. [123]

To assess in vitro extracellular IN inhibition, the McColl et al. method was used, and the most active compounds of the entire series were those with IC50 values between 13 nM (compound 76) and 31 nM (CA IC50 = 10 nM). Additionally, all of the discovered compounds had their cytotoxicity evaluated, and derivatives displayed little to no cytotoxicity.[124].

Despite the fact that a number of medications are sold commercially, seasonal flu claims 0.29 to 0.65 million lives per year. Influenza viruses cause the flu, which is a communicable respiratory illness. It manifests as severe epidemics that differ from one another and have no discernible periodicity or pattern. For these reasons, it is crucial to continuously work on developing new medications to treat this disease. Osman and his colleagues developed a new method to create bioactive compounds in 2019. They combined two bioactive parts into one molecule to create compounds with both antibacterial and antiviral properties. The team had previously investigated the combination of coumarin scaffolds and thiazole moiety, which

resulted in molecules with antibacterial and antiviral properties. This prior investigation helped to determine the potential of the combination of the two bioactive parts.[125]

The ability of oxidized coumarins to combat viruses may be one of their benefits. In fact, independent of the strain heterogeneity, coumarin derivatives may have an impact on intracellular redox-sensitive pathways important for viral replication due to their antioxidant activity. It has been investigated whether coumarins can be used as anti-hepatitis drugs.. Tsay and his team conducted a study to assess the efficacy of several synthetic imidazole-coumarin conjugates in combating the hepatitis C virus (HCV). The results revealed three compounds with significant antiviral activity against HCV, as evidenced by their EC50 values ranging from 5.1 to 8.4 M and selective indices (SI = CC50/EC50) greater than 20. [126]

3.11 Anti-tubercular Activity:-

Natural Analogues :- It has been investigated whether the natural substance coumarin, which is found in various plants such as tonka beans,and bison grass, sweet clover possesses any anti-tubercular properties Effective therapies are still being sought after due to the rise of drug-resistant forms of tuberculosis caused by Mycobacterium tuberculosis.

Coumarin derivatives may display anti-mycobacterial activities, according to several studies, making them prospective candidates for the creation of fresh anti-tubercular medications. Prior reaching my knowledge threshold in September 2021, the following major findings from study are presented:Action mechanism: Uncertainty exists regarding the specific mechanism by which coumarin exerts its anti-tubercular effects.[127]

Mechanism of action: It is still unclear exactly how coumarin works to prevent tuberculosis. However, some research points to the possibility that it might damage the mycobacterial cell wall, obstruct essential enzymes, or alter Mycobacterium tuberculosis's cellular metabolism. Animal research Positive findings from animal research suggest that some coumarin derivatives have strong anti-tubercular efficacy in vivo. These investigations are essential for determining the possible effectiveness of coumarin derivatives as anti-TB substances in living things. Clinical studies: There may not have been any completed clinical studies examining coumarin derivatives as a TB therapy as of my most recent update. Preclinical research, however, lays the foundation for prospective future clinical trials to assess the safety and effectiveness of derivatives.[128]

Mycobacterium tuberculosis inhibition: According to some study, the bacteria that causes tuberculosis (TB) can be inhibited by coumarin derivatives. The vital metabolic pathways of the bacteria may be disrupted by these compounds.

Synergy with Existing Drugs: Coumarin derivatives have been looked into for their potential to boost the effectiveness of currently available anti-TB medications. Treatment for tuberculosis may be more successful when combined with regular antibiotics and coumarin chemicals. Effects on Immunomodulation: Some coumarin derivatives have demonstrated effects on immunomodulation, which may be significant for the treatment of tuberculosis. Compounds that can strengthen the host's immunological response may be helpful in treating the infection because

TB frequently impairs the immune system.[129]

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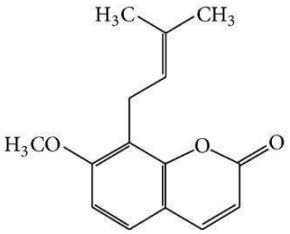

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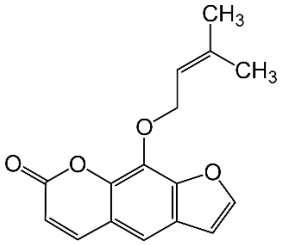

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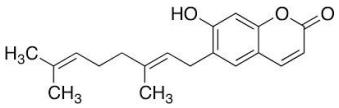
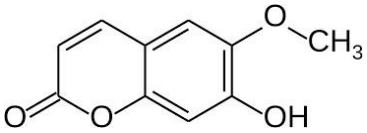
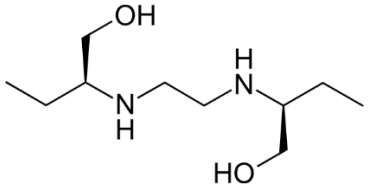


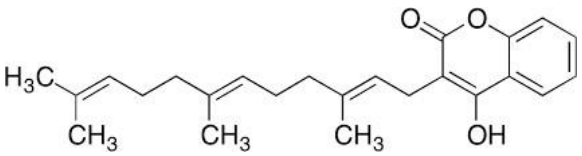
Ostruthin



Scopoletin



Ethambutol

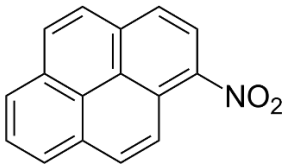


Ferulenol

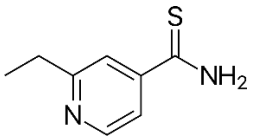
Fig. 18

Synthetic Analogues- N-containing heterocyclic compounds have been a subject of interest for medicinal chemists for a long time due to their varied biological activities. Pyridine is one of these heterocyclic compounds that has become well-known in medicinal chemistry due to its capacity to influence living organisms' enzymes, which ultimately aids in boosting the compound's pharmacological activity (Farhanullah et al., 2017). Additionally, pyridine-based substances like isoniazid and ethionamide are anti-TB medications. These findings prompted to combination of pyridine and coumarin in the assumption of creating elite molecular templates with improved anti-TB efficacy.[131] Additionally, coumarin and pyridine were

combined to create some unique chemical scaffolds that have powerful biological effects, including CNS depressants and antibacterial and antifungal properties. Two of the compounds that were evaluated, with MICs of 62.5 and 100 g/ml, respectively, demonstrated rather modest activity against the H37Rv strain. Other compounds were deemed less effective, with some showing no activity at all against H37Rv strains. Coumarin-pyridine hybrids stood out for their superior anti-TB properties. The findings suggested that these coumarin-pyridine combinations warrant further investigation. Structurally, it was found that incorporating a di-OCH3 group into the benzene ring of coumarin and coupling it with a benzofuran pyridine moiety enhances the anti-tubercular efficacy.[132]



Nitropyrene



Ethionamide

Fig. 19

DISCUSSION & CONCLUSION:-

Numerous organic substances having coumarinic nuclei have been shown to have a range of biological functions. Isomeric flavonoids and coumarins may have an impact on processes pertaining to free radical-mediated damage as well reactive oxygen species (ROS) development and scavenging. Coumarin has anti-inflammatory and tissue edemareducing properties. Additionally, coumarin and its 7-hydroxy derivative prevent the production of prostaglandins. Natural substances like fraxetin, esculetin, daphnetin and other Closely related derivatives of coumarin. known for being able to prevent the enzymes cycloxygenase and lipoxygenase as well as the neutrophil-dependent superoxide anions. Numerous researchers have invested a lot of time and energy into creating new substituted heterocyclic coumarin rings, primarily at the 3-, 4-, and/or 7-positions, due to the great importance of coumarin derivatives. The coumarin derivatives, either naturally occurring or synthesized, have anti-inflammatory and antioxidant properties (Fylaktakidou et al., 2004). The current state of innovative anti-cancer agent development using coumarin scaffolds .A class of polyphenolic chemicals generated from plants is called coumarins.

Due to their extensive pharmacological characteristics, Natural coumarins are highly valuable and are sought after by medicinal chemists For additional modifications to the backbone structure testing as various potential Curing agentNumerous coumarins and their derivatives have qualities that inhibit enzymes and have diabetic, hypertensive, tumor, viral, inflammatory, and oxidant actions. Pertaining to the creation of newly extracted coumarin analogues with better activity as well as to assess its mechanism of action and any potential adverse effects, it is essential to take advantage of key structural properties found in coumarin molecules. The therapeutic activities of the resultant compounds are significantly impact by the different replacements in the coumarin nucleus. It has been determined via study of many coumarin derivatives created by various researchers and their activities that the coumarin ring has fused with other rings. These compounds are employed to produce a range of important molecules

that act as building blocks for the development of novel medications due to the synergistic biological actions of both rings. Despite the identification of various coumarin derivatives with specific biological activities, the task at hand is to create novel derivatives that exhibit high specificity for additional pharmacological targets. Furthermore, it is crucial to elucidate their mechanism of action to develop new therapeutic medicines. When several compounds are combined with coumarin, their results may be similar or distinct.

For numerous years, it has been proven that coumarin and its related compounds possess great therapeutic potential. These compounds are sourced from a diverse range of natural sources, and novel coumarin derivatives are frequently discovered or synthesized. Many of the basic molecule derivatives of coumarin have been recognized for over a century. Their crucial function in the biology of plants and animals hasn't, however, been fully understood. The research reported makes it clear that coumarin and compounds linked to coumarin are a rich source of potential medicines candidates in terms of their safety and efficacy.

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