CHAPTER 10

Coumarin as a Potential Plant Metabolite Offering Diverse Range of Anti-Inflammatory and Therapeutic Effects

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SUMMARY

Coumarins are identified as a benzopyrone family member. All of which are made up of a benzene ring linked to a pyrone ring. Particularly, the physiological, bacteriostatic, and pharmacological properties of these compounds make them appealing for backbone derivatization and screening as new therapeutic agents. Coumarins act as anti-inflammatory substances by different mechanisms including inhibition of COX (cyclo-oxygenase pathway) and LOX (lipoxygenase pathway), decreasing edema development that is triggered by phagocytosis and blocking iNOS. Coumarins are known as secondary plant metabolites have also shown appreciable anti-bacterial activity. In-vitro and in-vivo studies have attested that coumarin is useful to treat diabetes by its predominant anti-oxidant and anti-inflammatory pathways, offering improvement of pancreatic function, rectification of abnormal insulin signaling, inhibition of PTP1B and alpha-glucosidase inhibitory pathways. It has also been documented that natural and synthetic coumarins may have the ability to inhibit acetylcholinesterase activity, offer neuroprotection, combat oxidative stress, and quench the free radicals' evoked localized or systemic damage. Therefore, it can be stated that coumarins may have the potential to act as promising candidates in the treatment of Alzheimer's disease. Coumarin has shown promise as a potential inhibitor of cellular proliferation in various carcinoma cell lines. Coumarin inhibited cell proliferation in a gastric carcinoma cell. Based on the aforementioned diverse range of insight into the mechanism for the effectiveness of coumarin's anti-inflammatory, cardiometabolic, neurodegenerative disorders and cancer protective potential highlight the precious pharmacological profile of coumarin in the diverse nature of disorders.

INTRODUCTION

Coumarin was first secluded in 1822 and combined in 1868. The Food and Medication Organization ordered it as a classification 1 cancer-causing agent and hepatotoxin during the 1950s in view of creature research. Nonetheless, considering new creature research, this might should be changed. A few coumarin subsidiaries displayed anticoagulant, tumoristatic, and immunostimulant properties (Zhao et al., 2021). Tonka beans, sweet clover, woodruff, oil of cassia, and lavender all contain coumarin, a normally happening part of medicinal oils. Coumarounaodorata is the name of the plant. In 1822, Voleg got coumarin from the tonka bean (Dipreryxodorata) and cleaned it. Perkin later combined it in 1868 (Casley-Smith & Casley-Smith, 1986). From that point forward, there a plenty of information with respect to its properties and expected applications.

Coumarin is otherwise called 2H-l-benzopyran-2-one, 1,2-benzopyrone, cis-o-coumarin corrosive lactone, coumarins anhydride, o-hydroxycinnamic corrosive and lactone. Coumarin is an individual from the benzopyrone gathering of mixtures. These are comprised of a-pyrone and melded benzene rings. Coumarin can be delivered by acids, catalysts, or bright (UV) radiation, yet it normally happens as a scentless complex formed to sugars and acids. In view of the presence of free coumarin in its organization, feed has a particular smell. Coumarin mixtures' antispasmodic properties have been utilized to treat different circumstances, including malignant growth, bums, brucellosis, and rheumatic illness as shown in Table 1. With a sub-atomic load of 146.15, coumarin is a dreary, sparkling substance with a wonderful and unmistakable smell. It bubbles at 303°C and has liquefying point of 68-70°C. Chloroform has a most extreme UV ingestion of 272 nm for coumarin. It breaks down promptly in oils, ethanol, and chloroform yet just sparingly in bubbling water and scarcely in 20 °C virus water. Coumarin is insoluble in water (Annunziata et al., 2020).

STRUCTURE ACTIVITY RELATIONSHIP

Both coumarin and 4-hydroxycoumarin have no anticoagulant properties. Link, who was a pioneer in isolating and characterisingbis' hydroxycoumarin (dicoumarol) from

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sweet clover, came to the conclusion that three minimum prerequisites for anticoagulant action are a bis molecule, a 4-hydroxy group, and a 3-substituent (Chen & Walsh, 2001). Coumarin's construction is obtained from cinnamic corrosive through ortho-hydroxylation, trans-cis isomerization of side chain twofold bond. Since change is steady or can't cyclize, isomerization should happen, and the protein isomerase is locked in (Jain & Joshi, 2012).

Table 1. Coumarin as its derivative

Drug	Toxicity	Applications
Coumarin	LT	Sweetener fixative flavor
4-hydroxycoumarin	Anticoagulant	Production of dicumarol and Warfarin
3,4 dihydroxycoumarin	LT	Perfume industry
Warfarin	Anticoagulant	Rodenticide
Flavone and acetic acid	LT	Cancer therapy

Table 2. Classification of Coumarin

Coumarin Types	Examples
Simple coumarin	Coumarin, Novobiocin, Coumermycin, Fraxin
Furanocoumarin	Umbelliferone, Imperatorin, Psoralen, Methoxsalen
Dihydrocoumarin	Anthogenol, Felamidin
Phenyl coumarin	IsodisparB, dispardiolB, mammeaA/AB cycloE,mammea,dioxalanocycloF,disparinolD, disparpropylinol B
Bicoumarin	Dicoumarol

RING-CHEMISTRY

Coumarins (also called 1,2-benzopyrone) are a vast category of plant-derived phenolic compounds that consist of fused benzene and a-pyrone rings. Around 1300 have been discovered, mostly as secondary metabolites in green plants, fungi, and bacteria. The odor of the prototype chemical is pleasant. Substitution can take place at any of the six eligible locations. Substitution and conjugation provide numerous permutations, which may well explain why several coumarinic derivatives exist in nature (Rawat & Reddy, 2022).

CLASSIFICATION OF COUMARIN

Based on the chemical makeup of the substances, six types of natural coumarins are the most common classifications as mentioned in Table 2 (Venugopala et al., 2013).

SOURCES OF COUMARIN

Yet passed all on through all bits of plant, the coumarins occur on the main levels in the regular items (Bael normal items (Aegle marmelos), Tetrapleura tetraptera (Mimosaceae), bilberry, and cloudberry), seeds (tonka beans) (Calophyllum cerasiferumVesque or Calophyllum inophyllum Linn) followed by the roots (Ferulago campestris), leaves (Murraya paniculata), Phellodendron amurense var. wilsonii, and plastic of the tropical rainforest tree Calophyllum teysmannii var. inophylloide green tea and different food sources like chicory. They are moreover found at huge levels in a couple of reviving oils, for instance, Cinnamon bark oil, and lavender oil. The pervasiveness of coumarins in different plant parts could be impacted by natural circumstances and occasional movements. In spite of the fact that ideas incorporate plant development controllers, bacteriostats, fungistats, and surprisingly, side-effects, the capability of coumarins isn't totally clear (Bansal et al., 2012).

In most plant domains, the blends known as coumarins can be found. Cinnamon bark oil (7,000 ppm) and lavender oil are instances of restorative balms with high obsessions. As per the survey, coumarin can likewise be found in regular items like cloudberry and bilberry as well as food things like green tea. Most coumarins can be tracked down in high plants, with Rutaceae and Umbelliferone giving the best stockpile. In spite of the fact that coumarins can be tracked down in any piece of the plant, the natural items with the roots, stems, and leaves have the greater part of them. The occasion in different pieces of the plant can be affected by natural circumstances and periodic developments. Six unadulterated minor coumarins have as of late been found in the dirt bark results of Calophyllum dispar (Clusiaceae). As per the audit, a portion of the 200 types of the Calophyllum class are used in regular medicine. Some normal coumarins have been found in microorganisms, regardless of the way that most of them were taken from higher plants. Instances of critical coumarin people that have been taken out from microbial sources incorporate Novobiocin from Streptomyces, as well as aflatoxins from Aspergillus species (Zhao et al., 2012).

Distribution Among Plant Organs

Coumarins have been found to accumulate more in fruit seed coverings and oil tubes than in other plant organs, according to the study. Pastinaca sativa is one such example. The researchers also discovered that Heracleumlanatum seeds. Archangelica had significantly higher coumarin contents than fruit tissues, which had significantly lower amounts. Certain plant species secrete coumarins on the surface of their leaves. Coumarins, according to studies, also play a distinct role in plant defense mechanisms, are found in higher concentrations in spring leaves than in autumn leaves, and are found in younger leaves rather than older leaves. Many plant species, which include Pimpinellaanisum, Psoraleabituminosa, Pastinaca sativa, Apiumgraveolens, Heracleumlanatum, and Ferula communis, var. glauca, exhibit this phenomenon more pronouncedly than others. Coumarins are flavoring and fragrance agents found naturally in Cinnamomumcassica, Anthoxanthumodoratum, and Dipteryxodorata (Annunziata et al., 2020).

Coumarin levels in ground cinnamon ranged from 5 to 7670 mg/kg, while levels in dry cinnamon ranged from 9900 to 12180 mg/kg. Surangin B, surangin C, are active coumarins found in M.siamensis. Coumarins were discovered in significant amounts in cinnamon bark oil (7000 respectively), as well as lavender oil. Green tea, cloudberry, and bilberry have all been found to contain coumarins. Surangins A and B have been revealed in Triana and Mammea longifolia (Wight). According to the study, bergapten concentration levels in Apium graveolens differed from leaf to petiole. Bergapten concentrations also showed a seasonal trend, increasing during the seedling stage and decreasing at maturity. Furthermore, older parsley leaves contain bergaptol-O-methyltransferases,

which are only found in furanocoumarins. Coumarins have a variety of biochemical and pharmacological phytotoxicities. Plant species from the Rutaceae and Umbelliferae families were the primary sources of coumarin reports. Coumarin is found in varying amounts in many plant organs, with fruits having the highest percentage, followed by roots, stems, and leaves. According to the study, the medicinal plant Artemisia capillaris contains a variety of coumarins, including scopolin, scoparone, esculetin, scopoletin, umbelliferone, and isoscopolin. Aflatoxin was discovered within Aspergillus species, while Streptomyces contained coumarins such as novobiocin and coumermycin. (Hussain et al., 2019).

COUMARIN-BASED ANTI-INFLAMMATORY PHYTOCONSTITUENT

The anti-inflammatory based phytoconstituents are scopoletin and Fraxetin. Scopoletin has anti-cancer, anti-diabetic, anti-hypertensive and nephroprotective properties. The antitumor action of scopoletin is due to the induction of multiple signal transduction pathways, including cell proliferation inhibition, cell cycle arrest, and apoptosis induction (Table 3). While Fraxetin has anticancer, antioxidant, anti-inflammatory and antidiabetic properties. It regulates the cell cycle by modulating crosstalk between STAT3 and Skp2/P27. It suppresses the proliferation of COAD cells by intrinsic apoptosis pathway and inhibits the JAK2/STAT3 pathway by targeting pivotal tyrosine residues.

COUMARIN'S ROLE AS A NATURAL BIOACTIVE DRUG

There have been many studies on chemicals with biological activity, but many of them have poisonous, carcinogenic, or mutagenic characteristics that make them unsuitable for therapeutic application. Today, it is feasible to alter the chemical structures of active chemicals to create substances with increased therapeutic activity and decreased toxicity. There are numerous phytochemicals with biological activity that can have therapeutic effects in herbs and herbal extracts. Many herbs can boost the immune system and offer some protection against cancer.

Coumarins are normally synthetics that can be found in an extensive variety of plant sources. Plant coumarins' long transformative relationship with various creature species and different life forms might make sense of their remarkable scope of biochemical and pharmacological effects in mammalian and other natural frameworks. The coumarins explored have a large number of organic properties and effects on different cell frameworks. To more readily comprehend how these coumarins work, a wide scope of natural properties ought to be assessed (Stefanachi et al., 2018). Coumarins are significant cell reinforcements, compound inhibitors, and risky substance forerunners in plant natural chemistry and physiology. Besides, these atoms take part in the exercises of plant development chemicals and development controllers, notwithstanding the administrative control of breath and photosynthesis, as well as contamination safeguard. Coumarins are calming, cell reinforcement, antiallergenic, hepatoprotective, antithrombotic, antiviral, and anticarcinogenic. Since they are phenolic compounds, hydroxycoumarins are productive metal chelators and free extreme scroungers. They are strong cancer prevention agents equipped for separating chains. Coumarins have many biochemical and pharmacological exercises, some of which propose that particular individuals from this compound class might essentially affect the capability of various mammalian cell frameworks (Kostova, 2005).

We made a number of new 1,4-thiazepines that were fused with coumarin using a straightforward method as part of our continuing research on the formation of bioactive coumarin compounds. The cell reinforcement and cytotoxic properties of the objective mixtures and 3-(2-hydroxybenzylidene) chroman-2,4-dione intermediates were utilized to assess their natural movement. The 1,1-diphenyl-2-picrylhydrazyl (DPPH) revolutionary searching strategy and the ferric

Table 3. Various coumarin derivatives isolated from plants (Bansal et al., 2012)

Sources	Constituents	Activities	Mechanism of action
Scopoletin	• Hydroalchoholic extract part of Justicia pectoralis • Ethyl acetate extract of Santolinaoblongifolia • Aqueous extract of Corydalis heterocarpa • Petroleum benzene / acetoacetate part of powdered stems of Erycibeobtusifolia	• Antimicrobial • Anticancer • Anti-inflammation • Antiangiogenesis • Anti-oxidation • Antidiabetic Antihypertensive • Hepatoprotective Neuroprotective	The antitumor action of scopoletin is due to the induction of multiple signal transduction pathways, including cell proliferation inhibition, cell cycle arrest, and apoptosis induction.
Fraxetin	• Dry extract of aerial part of Lingusticumlucidum • Aqueous infusion of aerial part of Biden tripartite	• Anticancer • Antioxidant • Anti-inflammatory • Antidiabetic • Antiobesity • Antimicrobial	It regulates the cell cycle by modulating crosstalk between STAT3 and Skp2/P27. It suppresses the proliferation of COAD cells by intrinsic apoptosis pathway and inhibits the JAK2/STAT3 pathway by targeting pivotal tyrosine residues.

diminishing cancer prevention agent power (FRAP) examination were utilized to assess the cell reinforcement movement. In the thiazepine series, the 4- methoxyphenolic compound 5d had the most grounded rummaging action. Furthermore, the cytotoxic assessment done with the MTT [3-(4,5-dimethylthiazol-2-yl)- 2,5-diphenyl tetrazolium bromide] uncovered that compound 5b is somewhere twice more successful than etoposide against the MDA-MB 231 cell lines as well as MCF-7 (Khoobi et al., 2011).

Nowadays, cancer is the second biggest cause of mortality worldwide or a critical clinical issue with considerable socioeconomic implications for healthcare. Chemotherapy is still a significant cancer treatment option in addition to surgery and radiotherapy. The development of innovative anticancer medicines like paclitaxel, docetaxel, imatinib, and sorafenib has greatly advanced cancer chemotherapy. Finding and creating more potent anticancer medications, however, continues to be very difficult because of the toxicity and drug-resistance issues with present chemotherapeutic treatments. Heterocyclic compounds stand out as a promising class of chemotherapeutic agents and anticancer treatment candidates. Because of their distinctive structural characteristics and wide range of biological activities, the formation of N and S-containing heterocyclic compounds, particularly thiazepines, has maintained the interest of researchers over the past two decades. Intriguing pharmacological characteristics, such as antiarrhythmic, antispasmodic and CNS actions, are found in aryl- and heteroaryl-fused 1,4- thiazepines, making them special structural type that offers potential synthesis targets. (Foroumadi et al., 2010).

Conversely, coumarin rings have been distinguished as an urgent primary part in various bioactive regular mixtures and meds. As far as anyone is concerned, be that as it may, no past reports of the coumarin-melded 1,4-thiazepine, which wires coumarin and thiazepine sections in a single particle, have been made (Nazarian et al., 2010). The multistep combination of 1,4- thiazepine utilizes various manufactured techniques, including expansion, buildup, coupling, adjustment, and thermolysis. Here, we might want to portray the union of novel 5 coumarins as a component of our continuous exploration of the blend of bioactive chromene or coumarin compounds utilizing a clear system in two stages and evaluating them for cell reinforcement and cytotoxic properties (Khoobi et al., 2011).

Coumarins are significant cancer prevention agents, protein inhibitors, and unsafe synthetic forerunners in plant organic chemistry and physiology. Additionally, these particles are related to the elements of plant development chemicals and development conditions, as well as their guideline. A few organically dynamic mixtures found in plants containing coumarins have been utilized in traditional medication for millennia. Coumarins are a huge compound class with anticancer, hostile to HIV, anticoagulant, spasmolytic, and antibacterial movement.

Among their numerous different benefits, coumarins' cancer prevention agent and antiproliferative properties stick out. In the long run, numerous fundamentally novel coumarin subsidiaries have been found to have huge in vitro and in vivo cytotoxic action. Besides, the inhibitory impact on incendiary cells seems, by all accounts, to be stronger than that of some other remedially possible medication. The helpful capability of the different coumarins is apparent, as some substituents are known to be committed for or increment their movement. (Kostova, 2005; Musa et al., 2008).

PHARMACOLOGICAL ACTIVITIES OF COUMARIN

Role of Coumarin in Inflammation

Inflammation is caused by a number of factors such as invasion of microorganisms, physical harm, damage due to ultraviolet rays and immunological responses. The typical symptoms of inflammation are reddening of skin, heat, swelling, and pain. Redness and heat are caused by increased blood flow whereas swelling occurs because of excessive movement of fluids and leukocytes to the site of inflammation. The release of chemical mediators and compression of nerves at the site of inflammation lead to pain. When inflammation becomes uncontrollable, it can progress towards the development of different diseases such as rheumatoid arthritis, chronic asthma, inflammatory bowel disease, multiple sclerosis and psoriasis (Grover & Jachak, 2015).

Plant based constituents are structurally the most diverse compounds and that's why they have drawn immense attention from medical experts for the development of medicines. One such example is coumarin, these active constituents are distributed widely in the kingdom of plants and are found in excessive amounts in different families such as Rutaceae and Umbelliferae. Different parts of these plant families like fruits, roots, stems and leaves are supplemented with large quantities of content. Coumarins show anti-inflammatory action in a number of ways such as by inhibiting COX and LOX, decreasing edema development that is triggered by phagocytosis and blocking iNOS (Borges et al., 2005).

In a study umbelliferone, that is a simple coumarin extracted from Justica pectoralisas showed a remarkable anti-edema effect in carrageenan-induced rat paw edema assay. A plant named Santolina oblongifolia contains four hydroxylated and methylated coumarins like esculetin, scopolin, herniarin and scopoletin, these mentioned coumarins inhibited thromboxane B2 (TXB2) release in platelets with the percentage of inhibition being slightly lower as compared to control drug (ibuprofen).

Another study shows that scopoletin, a renowned coumarin with anti-inflammatory action obtained from plant Erycibe obtusifolia has been proven to decrease the main symptoms of adjuvant-induced arthritis in rats by reducing the vascular endothelial growth factor, basic fibroblast growth factor and interleukin-6 overexpression in synovial tissues of adjuvant-induced arthritic rat models. Pyranocoumarins and prenyloxycoumarin obtained from the plant Ligusticum lucidum were evaluated in croton oil-induced ear dermatitis for their anti-inflammatory action. Another substitution on comarin nucleus with 7-(2', 3'-epoxy-3'-methylbutoxy) group exerts a strong anti-inflammatory effect but a saturated

pyrano-fused ring such as selidinin an (+)-praeruptorin A tends to have mild inflammation reducing effect (Pan et al., 2010).

Sesquiterpene containing coumarins from Ferula species such as Fukanemarins B, fukanefuronarins E-G, umbelliprenin and 8, acetoxy-5'—hydroxyumbelliprenin showed inflammation inhibiting effect (Menghini et al., 2010). The bioassay technique is used to isolate umbelliferone 6-carboxylic acid from Angelica decursiva as a potential inhibitor of nitros oxide formation in RAW 264 cells with an IC50 value of 72.98 micrograms/ml (Nazari & Iranshahi, 2011). Six coumarins named as scopoletin, scoparone, fraxetin, 4-methyl-umbeliferone esculin and daphnetin were checked in a study for their anti-inflammatory and anti-oxidant activity. It was found that daphnetin, scoparone and esculin were most active among these mentioned coumarin. Moreover, esculetin, daphnetin and fraxetin were designated as strong 5-LOX inhibitors with IC 50 values 0f 8.3, 75 and 20 micro-molar respectively. A study was conducted in which two coumarins name as columbinetin and libanoridin were separated from Corydalisheterocarpa. In the next step, these coumarins were tested for their anti-inflammatory effect in HT-29 human colon carcinoma cells. This study showed that libanoridine remarkably inhibited mediators responsible for inflammation such as iNOS, COX-2, TNF-alpha and IL-1 beta but columbianetin did not show any anti-inflammatory activity (Zhao et al., 2012).

Role of Coumarin as Anti-diabetic

Diabetes mellitus is one of a chronic metabolic disease that is defined by both fasting and postprandial hyperglycemia that occurs because of insulin deficiency or insulin resistance. For the reduction of diabetic complications and enhancing the function of the pancreas gland through anti-inflammation and anti-oxidation pathways, improving secretion of insulin and promoting action of insulin on its desired tissues, different cellular and metabolic targets can be taken into account (Fig 1).

Medicinal researchers always strive to find potent and prudent drugs for diabetes and its complications. Among the cases of diabetes, 90% are type 2 diabetic patients. So researchers are looking to find effective agents for type 2 diabetes that can decrease insulin resistance. For example, drugs that increase insulin sensitivity and enhance its effect, improve beta cell function or increase the immune system. Another approach is drawing attention to achieve hypoglycemia is to block the re-uptake of glucose in the renal tubules by inhibiting SGLT2 and promoting loss of glucose in the urine.

This study was focused on managing diabetes by coumarins and related mechanisms. It is proved by a number of in-vitro and in-vivo studies that coumarin can be used to treat diabetes by anti-oxidant and anti-inflammatory pathways, by improvement of pancreatic function, rectification of abnormal insulin signaling, inhibition of PTP1B and alpha-glucosidase. So, consequently, coumarins are valuable and should be further investigated and developed. Among coumarins, osthole and psoalen can target AMPK and activate it, thus enhancing glucose utilization by augmenting GLUT4 translocation to the plasma membrane. Actually, AMPK can initiate translocation of GLUT4 in the absence of insulin, so this strategy can be used to form drugs that enhance insulin action (Coughlan et al., 2014).

Moreover, it is important to determine whether all coumarins have this property. In short, it is proved that coumarins can be effective in the management of diabetes and its complications due to their biochemical and pharmacological properties, some of which are important from the therapeutic point of view. The pathogenicity of diabetes is multifactorial that's why it requires a multi-model therapeutic strategy. So, coumarin has a diverse range of targets that are responsible for its anti-diabetic effect. The literature describes that coumarin could be used as adjuvant therapy with other anti-diabetic drugs to treat diabetes and cardiovascular problems on the basis of integrative medicine that combines conventional treatment with evidence-based complementary therapies.

The final material which is obtained from in-vitro and in-vivo animal studies needs to be further interpreted cautiously, so it means there are still a lot of research areas that need to be explored. Therefore, research should be targeted towards rational development of prudent and more potential compounds that could be used as a professional treatment for diabetes and related complications. There are several varying baseline features such as age, gender, chronic social habits, ethnicity and other more complex in-vivo processes in humans so, thats' why it is not possible to make direct comparisons and generalizations. Moreover, emphasis should be placed on the pharmacokinetic related parameters (absorption, distribution, metabolism and excretion) for in-vivo development.

The recent studies regarding coumarin have represented remarkable improvements in basic parameters related to the physiology of insulin such as oral glucose tolerance test,

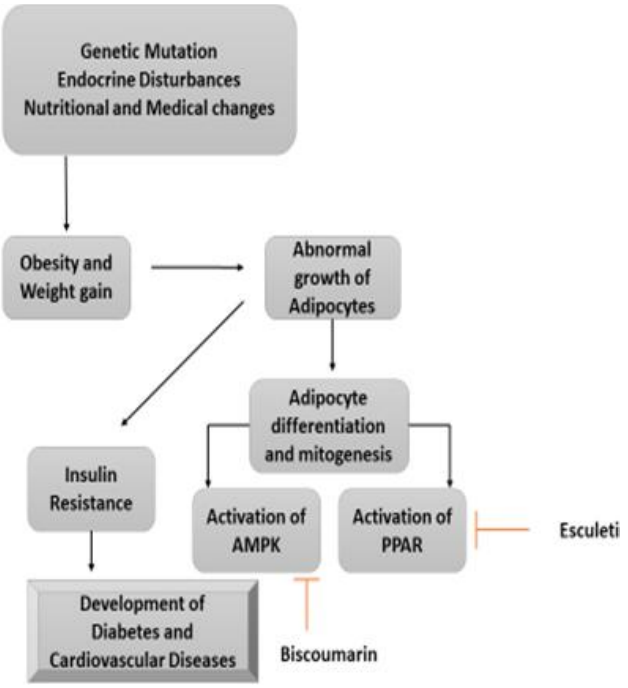

Fig 1. Mechanistic diagram of cardiometabolic diseases

fasting blood glucose levels, insulin levels and activity of some important proteins that take part in signaling and glucose transport named as IR, Akt, GLUT, AMPK, PPAR and some others aside from boundaries. The main pathway that leads towards these actions and receptors of coumarins and their derivatives and SAR needs to be investigated.

To conclude, the progress in the area of research has moved towards the separation or chemical design of advanced and useful agents with basic coumarin structures as potential candidates for diabetes and related complications. However, extensive research is still required before prudent and beneficial coumarin drugs are used in clinical setup (Li et al., 2017).

Role of Coumarin as Antibacterial

Coumarins are known as secondary metabolites, were shown to possess average to good efficacy as anti-bacterial agents. Coumarin compounds particularly those containing hydrocarbon substitutions, namely and ostruthin and ammoresinol, have a high antibacterial effect on gram-positive pathogens. An antibiotic obtained from a fungus named novobiocin has been found to be useful for inhibiting gram-positive and gram-negative bacteria. In addition, coumaermycin also has activity against bacterial infections. A study described that this compound can sufficiently cause a delay in DNA supercoiling of E.coli and this antibacterial effect is 50% stronger than novobiocin.

A biologically effective natural coumarin compound named imperatorin, isolated from Angelica dahurica and Angelica archangelica, was shown to possess an antibacterial effect against Shigella dysenteriae. Scopolin, ayapin, and scopoletin have shown antimicrobial activity against the head rot of sunflower. Moreover, scopolamine was found to possess a stronger antibacterial effect as compared to sclerotinia than other studied compounds (Prats et al., 2007; Basile et al., 2009; Koziol & Skalicka-Wonizak, 2016).

Role of Coumarin in Alzheimer's Disease

Diseases that deteriorate the nervous system such as Alzheimer’s disease, it is defined by a progressive loss of cognitive, behavioral, and social abilities, ultimately rendering a person unable to function independently (Goedert & Spillantini, 2006). Different factors can lead to the development of Alzheimer’s disease like the disruption of brain proteins which eventually results in modulating the functions of brain cells and initiating a chain of harmful events (Gella & Durany, 2009; Mustafa & Mohammed, 2021). This disease is also associated with a remarkable loss of cholinergic system related functions because of a deficiency in neurotransmitters such as acetylcholine in some specific parts of the brain which regulate learning and regular memory functioning (Greig et al., 2005). So, a drug that can inhibit acetylcholinesterase and/or butyrylcholinesterase could be used to treat this disease.

According to the literature, some natural and synthetic coumarins may have the ability to inhibit acetylcholinesterase, lessen oxidative stress, and quench damage-related free radicals. Furthermore, coumarins have the potential to protect neurons. Therefore, it can be concluded that coumarins may have the potential to act as promising candidates treating Alzheimer's disease (Hadjipavlou-Litina et al., 2007; Changwong et al., 2012). Coumarin congener named ensaculin 1 (KA-672), has newly been stated to have high therapeutic potential to suppress acetylcholinesterase (Mustafa & Mohammad, 2021).

Role of Coumarin as Anti-tumor

The biomedical research related to coumarin compounds has shown that these substances have a therapeutic potential for treating different types of cancer (Khalil & Mustafa, 2020). A number of studies were carried out on cancer present in the brain, prostate, skin, pancreatic cells, breast, and others. Among the coumarin compounds, ostiole has shown strong potential to suppress the metalloproteinase promoter and ultimately limit the spread of human breast cancer (Sashidhara et al., 2010). Furthermore, a natural derivative of coumarin named neo- tanshinlactone can decrease the progression of two estrogen receptor positive breast tumor cells. Interestingly activity of this derivative is approximately ten times higher as compared to tamoxifen.

Based on the hybrid structural strategy, antitumor medicines were formulated by combining two pharmacologically active structures i.e. coumarin and monastrol which resulted in the formation of a coumarin-monastrol hybrid. These hybrids were shown to have significant activity for MDB-MB-231 and MCF-7 (breast cell adenocarcinoma) cell lines. To investigate the principle behind the hybrid’s anticancer activity, different assays were carried out including apoptotic investigations, caspase-3 activation assays and cell cycle analyses. The activation of caspase-3 proceeded toward the death of both original and metastatic mammary tumor cells irrespective of estrogen receptor status (ER status).

Furanocoumarin such as psoralidin was isolated from the seeds of a plant known as Psoralea corylifolia (Zhao et al., 2005; Xiao et al., 2010). Such kinds of coumarins have indicated a strong cytotoxic effect against the cell populations HT-29 (colon tumor), SNU- 1, SNU-16 (gastric tumor) and MCF-7 (breast tumor). Other than this psoralidin has been indicated to cause cell death in both androgen dependent and independent prostate cancer cells along with the reduction in the development of PC3 xenograft carcinomas in mice.

Different mechanisms are responsible for the anticancer activity of coumarin-derived compounds including the deactivation of the telomerase enzyme, inhibition of protein kinase action, moreover, suppression of oncogene transcription. In addition, researchers found out that coumarins can halt cancer cell growth by stopping the cell cycle in the G0/G1 or G2/M phases along with changes in cancer cell p-glycoprotein. Furthermore, hydroxycoumarin compounds also have an anti-cancer effect by a mechanism that is responsible for the formation of free radicles and eventually results in oxidative stress and apoptosis. Besides this, coumarin derivatives were also able to suppress protein kinase 2 and ultimately prevent cancer cell growth.

Role of Coumarin in Obesity

Obesity is becoming a dangerous health problem and it is one of the biggest threats to human well-being all over the world. Different factors are involved in the pathogenesis of obesity such as endocrine disturbances, genetic mutations, nutritional and medicinal changes and many other related problems. Furthermore, obesity proceeds to number of other pathological conditions including diabetes, hypertension, hyperlipidemia and cardiovascular diseases (Ferrara & Kerbel, 2005).

The adipose tissue is the main connective tissue that actively takes part in insulin sensitivity and energy homeostasis. The basic function of this tissue is to accumulate excess nutrients in the form of triacylglycerol and their release as free fatty acids during fasting conditions. Adipose tissue secretes more than fifty hormones and signaling molecules, collectively named as adipokines and they are responsible for glucose metabolism, immunity and energy homeostasis. The changes in body weight proceed towards alterations in vasculature and metabolism. The change in body weight leads to changes in vasculature and metabolism. Adipokines can specifically elicit either pro-inflammatory or anti-inflammatory effects, eventually contributing to insulin resistance. Obesity causes the adipocytes to undergo abnormal growth that is identified by the excess number of fat cells (hyperplasic) or increased adipocyte volume (hypertrophic) and results in decreased insulin sensitivity and other related problems. In particular, adipokines can elicit either pro-inflammatory or anti-inflammatory properties, eventually contributing to insulin resistance. Obesity causes the adipocytes to undergo abnormal growth that is characterized by more numbers of fat cells (hyperplasic) or enhanced adipocyte volume (hypertrophic) and results in insulin resistance, lipid and other related problems. Excessive mitogenesis and differentiation are the basis of pathological adipocyte growth. So, the initiation and procession of obesity can be prevented by inhibiting the mitosis and differentiation of pre-adipocytes to adipocytes.

Different coumarins including sulphonate coumarin and biscoumarin were investigated for their potential to suppress the adipocyte differentiation in 3T3-L1 cells. Several compounds of these kinds inhibited the adipocyte differentiation in a dose dose-dependent pattern. Among these types of compounds, some particularly inhibited adipogenic differentiation and among these types of compounds, some particularly inhibited the adipogenic differentiation and also indicated lipolytic activity in mature adipocytes. The potential substances substitute the AMP-activated protein kinase ligand, therefore, the complex of these substances with AMPK possibly halts the anabolic pathways.

In the quest for screening of plant-based products for their anti-adipogenic potential, different pre-adipocyte cell lines, 3T3-L1 as an in-vitro system, the EtOAc fraction (that is obtained from the stem bark of Fraxinus rhynchophylla) were analyzed. Dence (Oleaceae) exhibited a remarkable inhibitory effect on the differentiation of adipocytes as this was examined by measuring fat accumulation through Oil Red O staining. Six different types of coumarins were isolated with the help of activity guided fractionation such as esculetin, scopoletin, fraxetin, fraxidin, esculin and fraxin.

Esculetin exhibited the strongest inhibitory effect on the differentiation of adipocytes followed by fraxetin among the isolated coumarin in the above mentioned study. Detailed studies using treatment interval explained that esculetin showed inhibitory activity on the differentiation of adipocytes if treated within two days after differentiation induction. Afterward, studies proceeded towards the assessment of the esculetin effect on peroxisome proliferator activated receptor gamma (PPAR) which is one of the early adipogenic transcription factors. It was observed during the study trial that esculetin blocked the induction of PPAR protein expression and inhibited the differentiation of adipocytes induced by PPAR agonist (troglitazone). Therefore, it was concluded from results that esculetin, an active compound obtained from Fraxinus rhychophylla blocked the early step of adipogenic differentiation through inhibition of the PPAR-dependent pathway.

Role of Coumarin in Non-alcoholic Fatty Liver Disease

Non-alcoholic fatty liver disease is an ongoing disease that can cause fibrosis or cirrhosis and cancer of the liver. Fatty liver disease and decreased insulin sensitivity are inter-linked and can be found in 70-100% of the obese population. The pathological basis of liver disease is not fully clear but excessive fat storage and free radicals production seem to be directly involved in its initiation and progression. Moreover, overindulgent and intake of excessive dietary fats lead to decreased insulin sensitivity, enhanced free fatty acids delivery to the liver and gene mutations responsible for lipid metabolism, all of these factors cause fat accumulation in the liver. So, newer studies are being carried out to assess whether phytochemicals present in food have useful effects on liver metabolism, such as reducing fat storage in the liver and improving insulin sensitivity.

The current study was carried out to investigate the impact of coumarin on high fat diet induced fat storage in C57BL/6J mice. Liver steatosis is commonly found in overweight people. The liver steatosis mainly occurs due to body adiposity, this interpretation shows that obesity related factors can be managed by reducing fat mass. The results of current studies have shown that the weight gain and adipose fat mass induced by high fat diet model were sufficiently decreased by coumarin intake. Typically, fat mass storage can be decreased by reducing food intake, but later it was observed that the intake of food was the same among the experimental groups of animals in the current study. In addition to this, it was also found that epididymal fats weighed less in the group of animals that received coumarin treatment as compared to the high fat diet-fed group of animals. Adipocytes release a hormone that is called leptin and it plays an important role in the regulation of appetite and energy consumption, moreover, the amount of leptin strongly correlates with the body fats in high fat diet group, that's why serum levels of leptin are considered as indicator of body fat storage. It was found that coumarin significantly reduced serum levels of leptin which were raised by high fat diet intake. Therefore, it can be

deduced from this study that coumarin intake can lower high fat diet induced body weight gain and fat accumulation.

Another study demonstrated that there is a close link between non-alcoholic-fatty-liver disease and hyperlipidemia and these problems proceed toward the lipids and free fatty acids excess in hepatic cells and eventually end up with liver failure. Though, in the current study, triacylglycerol levels were similar among all the experimental groups but supplementation with coumarin reduced serum levels of triglycerides, free fatty acids and apoB significantly. The findings of this study were consistent with the results of another study that documented that intake of coumaric acid for 8 weeks decreased high fat diet induced rise in rats. Other than this, one more study confirmed that serum total cholesterol (TC) levels were lowered by intake of a substituted coumarin, 7, 8-dihydroxy- 3-(4-methylphenyl) coumarin in rats. So, it can be stated that the accumulation of lipids in the liver was prevented by the normalization of serum lipids level in coumarin treated group.

The liver is the main organ for lipid metabolism. It was indicated by pre-clinical and clinical studies that liver steatosis occurs because of excess of resultant products of de novo synthesis of fatty acids (Li et al., 2017). According to another study, histological examination revealed that high fat diet caused a noticeable rise in lipids droplet numbers, this was treated by coumarin supplementation. Moreover, it was also found that supplementation with coumarin decreased triacylglycerol, total lipids levels and total cholesterol levels significantly and reduced the effect of enzymes, responsible for liver fatty acid production (i.e. Fatty acid synthase and malic enzyme). Whereas fatty acid synthase (FAS) speeds up the production of long-chain fatty acids from acetyl-CoA and malonyl CoA in the presence of NADPH. Malic enzyme (ME) is a lipid-forming enzyme responsible for providing NADPH to biosynthesize fatty acids. If FAS and ME activity has been reduced then it will decrease the amount of long-chain fatty acids required for triacylglycerol production. Literature has shown that coumarin can decrease liver fatty acid synthase and malic enzyme action in high fat diet induced model and it possibly is the cause of decreased lipid storage in the liver.

These studies have documented that coumarin would be a treatment option for high fat diet induced liver steatosis, that probably achieved by controlling genes responsible for lipid production. Therefore, such findings support that coumarin can be helpful in the amelioration of liver steatosis.

Role of Coumarin in Hyperlipidemia

Hyperlipidemia is a disease that occurs due to high LDL or hypercholesterolemia and it is one of the most common causes that leads to the initiation of atherosclerosis and resultant cardiac vascular disease. This disease is simply defined as high blood levels of lipids or fats. Several factors are being responsible for the development of atherosclerosis such as endothelial damage, hyperlipidemia, inflammatory and immunologic factors, hypertension, smoking and plaque erosion or rupture. Symptoms of atherosclerosis do not appear until stenosis of plaque reaches 70-80% of the vessel's diameter. This problem begins when the underlying endothelial damage happens, that apparently occurs due to the loss of nitric oxide within the endothelium. These factors become the reason for increased inflammation around the dysfunctional site, surrounding the site of dysfunction, allowing the lipids storage in the the most inner layer of the endothelial wall. Lipids accumulate within the the most inner layer of the endothelial wall. These excessive lipids are later eaten by macrophages, progressing to the development of foam cells. Therefore, cholesterol formation within foam cells leads to consequent dysfunction of mitochondria, apoptosis, and eventually necrosis of underneath tissues. Furthermore, smooth muscle cells encapsulate these foam cells or debris and form fibrotic plaque that hinders the destruction of lipids in underlying tissues.

A study was conducted to evaluate different coumarins for their cholesterol-lowering effect in high fat diet fed rat model. This study trial was continued for four weeks and different parameters were checked such as increase in weight, daily food intake and feed efficiency. Biochemical parameters were also calculated including total cholesterol, total glycerides, low density and high density lipoprotein. Structure activity relationship of coumarins was also determined in this study by calculating the liver index, atherogenic index and cardiac risk factor. The study demonstrated that the high fat diet raised the concentration of total cholesterol, LDL and total glycerides and decreased HDL. Moreover, the study showed that all coumarins under test and standard statins drugs decreased cholesterol and increased HDL levels. Among these coumarins, 7-methoxy coumarin was the strongest cholesterol-lowering coumarin and exhibited reversal of cardiac risk factor, and the liver and atherogenic indices.

CONCLUSION

This chapter covers natural coumarin lead compounds and their broad pharmacological properties. Their physiological, bacteriostatic and anti-tumor activity makes these compounds attractive for further backbone derivatization and screening as novel therapeutic agents. Natural coumarins are of great interest due to their widespread pharmacological properties, and this attracts many medicinal chemists for further backbone derivatization and screening them as several novel therapeutic agents.

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