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COUMARINS AS PROMISING ANTICANCER AGENTS: A COMPREHENSIVE OVERVIEW OF MECHANISMS AND THERAPEUTIC POTENTIAL

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ABSTRACT

Cancer continues to represent a major global health burden, necessitating the discovery of therapeutic agents with improved efficacy and reduced toxicity. Coumarin and its derivatives, classified as benzopyrone-based natural compounds, have emerged as promising candidates due to their diverse pharmacological activities, particularly their anticancer potential. These molecules exert their effects through multiple cellular mechanisms, including modulation of apoptotic pathways, inhibition of tumor cell proliferation, interference with oncogenic signaling networks, and enhancement of responses to standard chemotherapeutic agents. Key derivatives such as osthol, dicoumarol, and biscoumarins have demonstrated significant inhibitory activity against a variety of malignancies, including colon, gastric, melanoma, and hematological cancers. Additionally, combining natural substances like curcumin in a synergistic way may enhance therapeutic results. The latest developments, molecular understandings, safety concerns, and potential applications of coumarin-based anticancer treatments are compiled in this review.

KEYWORDS: Coumarin derivatives, Anticancer activity, Osthol, Dicoumarol, Apoptosis.

INTRODUCTION

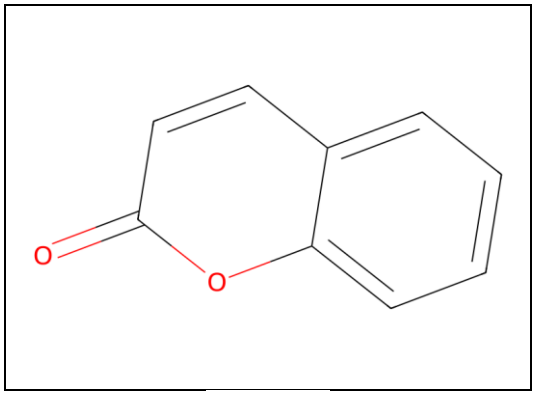
Cancer remains a major global health concern, contributing significantly to illness and death worldwide. Among the various types, colon and stomach cancers are particularly prevalent, and their prognosis largely depends on the stage at which they are diagnosed.[1] Early-stage detection offers a high chance of successful treatment, whereas late-stage disease is associated with poor survival outcomes, emphasizing the need for improved therapeutic strategies. Conventional anticancer drugs often suffer from limitations such as toxicity, resistance development, and lack of selectivity, which drives the ongoing search for safer and more effective alternatives. Natural compounds have gained considerable interest in oncology research, with coumarins emerging as promising candidates.[2] Coumarin and its derivatives are benzopyrone-based compounds naturally present in many plants and have demonstrated diverse biological effects, including anti-inflammatory, antioxidant, anticoagulant, and significant anticancer activities. Various derivatives such as osthol, dicoumarol, and biscoumarins have shown significant potential in inhibiting the growth of cancer cells by inducing apoptosis, disrupting cellular signaling, and improving the effectiveness of existing chemotherapeutic agents like 5-fluorouracil.[3] However, because of indications of hepatotoxicity and carcinogenicity in animal studies, the safety profile of coumarin has been challenged. These effects are not consistently observed in humans due to differences in metabolic pathways, particularly coumarin 7-hydroxylation, which reduces toxic metabolite formation.[4] Meanwhile, curcumin, another natural compound, has also shown synergistic anticancer potential with coumarin derivatives by modulating oxidative stress and inflammation. This review focuses on the therapeutic relevance, mechanisms, and future potential of coumarin derivatives in cancer treatment.

Cancer

Cancer is a complex disease characterized by the uncontrolled and persistent division of cells, resulting from genetic disruptions within the cell.[5] Under normal conditions, cellular growth, division, and death are governed by a tightly regulated network of genes located on chromosomes. These genes ensure that cells divide

only when necessary and perform their functions correctly. However, when cells are exposed to various harmful influences such as radiation, chemicals, viruses, or random replication errors, alterations in the DNA may occur. Although cells possess DNA repair mechanisms designed to identify and correct such damage, these systems are not always completely effective.[6] Failure in repair can lead to permanent genetic changes that compromise cellular control and allow abnormal cell proliferation. In addition to direct genetic mutations, changes in gene expression can also result from epigenetic modifications. Epigenetic mechanisms, including DNA methylation and histone acetylation, regulate how genes are turned "on" or "off" without altering the DNA sequence itself.[7]

Three major categories of genes are closely associated with cancer development. Proto-oncogenes are normal genes involved in cell growth, but when mutated or excessively expressed, they become oncogenes, driving cells to divide uncontrollably.[8] Examples include RAS and MYC. Tumor suppressor genes, such as TP53, normally function to inhibit excessive cell proliferation and promote DNA apoptosis; their loss removes essential growth restraints. DNA repair genes are responsible for correcting errors during replication, and defects in these genes increase the likelihood of accumulating harmful mutations. Cancer cells possess several unique abilities that distinguish them from normal cells.[9] They can produce their own growth signals, resist programmed cell death, and maintain telomere length to support limitless replication. Furthermore, they have the capacity to invade surrounding tissues and spread to distant organs through the bloodstream or lymphatic system-a process known as metastasis.[10] These properties collectively contribute to the genetic instability, adaptability, and aggressive nature of cancer cells.



Coumarin.

Chemistry

Coumarin is a prominent representative of a large class of naturally occurring phenolic compounds collectively referred to as the coumarin family.[11] Chemically, coumarin consists of a benzene ring fused to a 2-pyrone ring, giving rise to a distinctive heterocyclic scaffold. In natural sources, the coumarin nucleus frequently contains oxygen substituents, especially at the C-7 position, while modifications may also be present at C-5, C-6, and C-8. These hydroxyl groups are commonly converted into glycosidic forms, which influence the solubility, transport, and overall biological behavior of the compound.[11] The structural diversity of coumarins in nature arises largely from enzymatic substitutions on the core ring system, creating a broad spectrum of derivatives with varied therapeutic potentials.[13] From a pharmacokinetic perspective, most coumarins comply with Lipinski's rule of five, indicating favorable absorption and membrane permeability properties that support their potential for development as oral drugs. Their optimized molecular size, lipophilicity, and hydrogen-bonding capacity make them capable of crossing biological barriers, allowing them to interact effectively with intracellular targets. Due to these features, coumarins have been extensively studied for diverse pharmacological activities. Well-documented therapeutic effects include anticoagulant action, where compounds such as warfarin have become essential in the management of thrombosis.[14] In addition, many coumarins exhibit anticancer, antioxidant, antimicrobial, antiviral, and anti-inflammatory properties. They are also known to inhibit various key enzymes, contributing to their regulatory effects on cellular metabolism and signaling pathways.

Despite these valuable pharmacological properties, coumarin has been surrounded by safety concerns. In 1954, the U.S. Food and Drug Administration imposed a ban on the use of coumarin as a flavoring agent in food due to evidence of liver toxicity in certain animal species.[15] Subsequent investigations, however, revealed that the toxicity of coumarin is highly dependent on metabolic pathways that differ significantly between species.[16] The therapeutic effectiveness and safety of coumarin compounds are strongly influenced by their structural variations and substitution patterns. Even small modifications in the coumarin ring system can lead to significant changes in biological activity. Therefore, understanding the relationship between structure and function is crucial for designing new coumarin derivatives with enhanced therapeutic utility and minimal toxicity. The ongoing study of coumarins continues to highlight their promise as versatile pharmacophores, offering numerous opportunities for the development of novel drug molecules across a wide spectrum of clinical applications.[17]

Anticancer activities of coumarin

Chemotherapy remains one of the primary treatment strategies for managing and controlling different forms of cancer.[18] The chemotherapeutic drugs function through a variety of mechanisms, including direct interaction with DNA, inhibition of DNA replication and transcription, disruption of cell division, interference with cellular signaling pathways, and the targeting of specific molecular receptors involved in tumor progression. Over recent years, the direction of cancer therapy has increasingly shifted toward identifying

compounds that act more selectively on cancer cells, thereby minimizing side effects and improving therapeutic outcomes.[19] Among the diverse structural frameworks investigated for anticancer activity, coumarin and its derivatives have emerged as particularly promising. Coumarins are naturally occurring benzopyrone compounds that can be chemically modified to enhance their pharmacological potential. Numerous studies have shown that coumarin-based molecules exhibit significant anticancer effects across different tumor types. Their anticancer activity is often attributed to their ability to interfere with essential cellular processes, including cell cycle regulation, DNA repair mechanisms, and apoptosis signaling pathways.[20]

Coumarin derivatives can be broadly classified into several mechanistic categories. Some function as alkylating agents, forming covalent bonds with DNA and thereby inhibiting replication and transcription.[21] Others act as topoisomerase inhibitors, disrupting the enzymes responsible for uncoiling DNA during cell division, which leads to DNA strand breakage and cell death.[22] Additionally, certain coumarin compounds are known to induce apoptosis by activating specific intracellular pathways or by triggering oxidative stress, which promotes programmed cell death in cancer cells. This review focuses on coumarin-based anticancer agents reported in the past five years, emphasizing their structural modifications, biological activities, and molecular mechanisms of action. Special attention is given to their interactions at the enzymatic and cellular levels, as understanding these relationships is essential for designing more potent and selective therapeutic candidates. The potential of coumarin scaffolds as valuable leads in the development of next-generation anticancer drugs.[23]

Coumarins in Leukemia

Leukemia is a type of blood cancer that originates in the bone marrow, where blood cells are produced. It is characterized by the abnormal and excessive growth of immature hematopoietic precursor cells, which are unable to function as normal blood cells. As these malignant cells multiply, they gradually crowd out healthy cells within the bone marrow. This replacement of normal cells leads to a significant reduction in the production of essential blood components, including red blood cells, platelets, and mature functional white blood cells.[24] The decline in these cell populations results in several clinical symptoms and complications. Patients may experience severe anemia due to decreased red blood cells, a heightened susceptibility to infections due to low functional leukocytes, and increased bleeding tendencies because of platelet deficiency. In severe cases, these abnormalities can also contribute to breathing difficulties and compromised immune defense. Leukemia is broadly divided into two major forms: acute and chronic. Acute leukemia progresses rapidly, involving a accumulation of immature cells, and is more commonly observed in children.[25] It requires immediate medical attention due to its aggressive nature. On the other hand, chronic leukemia develops gradually and typically affects adults. Although some blood cells may partially mature in chronic leukemia, they remain dysfunctional and unable to perform their normal roles effectively.

The causes of leukemia are multifactorial, involving both genetic mutations and environmental influences. Changes in genes that control cell growth, differentiation, or programmed cell death can initiate the malignant transformation of bone marrow cells.[26] Additionally, exposure to ionizing radiation, certain chemicals, and viral infections has been linked to an increased risk of leukemia. Treatment strategies aim to control abnormal cell proliferation, restore healthy bone marrow function, and prevent complications. Common therapeutic approaches include chemotherapy, which targets rapidly dividing cells, radiation therapy, and bone marrow. Recent advances also include targeted and immunotherapeutic agents that act on specific molecular pathways involved in the disease. In recent scientific investigations, naturally occurring compounds such as coumarin derivatives have demonstrated promising anticancer potential. Notably, substances like esculetin and 7-hydroxycoumarin have exhibited cytotoxic and growth-inhibitory effects on leukemia cells, suggesting their possible role in future therapeutic development. Continued research into these bioactive compounds may contribute to the discovery of safer and more effective treatments for leukemia.[27]

Pharmacokinetics of Coumarins

After oral administration, coumarin and its derivatives are absorbed rapidly from the gastrointestinal tract. Their absorption behavior is closely tied to their physicochemical properties.[28] Coumarins have low aqueous solubility but are highly soluble in lipids, which enables them to move across the intestinal epithelial membrane primarily through passive diffusion. Although absorption from the gut is efficient, only a small fraction of the parent compound enters the bloodstream unchanged. This limited systemic availability is largely the result of extensive first-pass metabolism in the liver. Once absorbed, coumarin undergoes rapid biotransformation before reaching the systemic circulation. It is estimated that only about 2–6% of an orally administered dose appears in the circulation in its original form.[29] The predominant metabolic pathway involves oxidation mediated by the cytochrome P450 enzyme CYP2A6. This enzyme converts coumarin into its principal metabolite, 7-hydroxycoumarin. Following hydroxylation, the metabolite undergoes further conjugation, most commonly with glucuronic acid, resulting in the formation of 7-hydroxycoumarin glucuronide. These conjugates exhibit greater polarity and are therefore more easily eliminated from the body.[30]

Excretion of coumarin metabolites occurs mainly through the kidneys. The glucuronide conjugates are readily filtered and are found in significant amounts in the urine.[31] Only negligible traces of the unchanged parent compound are typically excreted. In individuals with normal metabolic and renal function, coumarin exhibits relatively efficient clearance, with metabolite elimination occurring over a short time frame. its pharmacological usefulness, especially in anticoagulant therapy, coumarin use is associated with notable adverse effects. The most clinically significant risk is hemorrhage, which may range from mild bruising to severe internal bleeding. Consequently, careful dose adjustment and regular monitoring of coagulation status are essential during treatment.[32]

Additional adverse outcomes may include disturbances in bone metabolism, which can contribute to decreased bone density with long-term use. In rare cases, skin necrosis has been observed, often linked to early therapy phases when clotting factor imbalance occurs. Coumarins also present specific risks during pregnancy because they readily cross the placental barrier. Exposure to coumarin derivatives such as warfarin during early fetal development has been associated with a condition known as warfarin embryopathy, characterized by skeletal abnormalities and developmental defects.[33] For this reason, coumarin-based anticoagulants are typically avoided during pregnancy, and alternative therapies are preferred. Coumarins are efficiently absorbed but undergo substantial hepatic metabolism, with renal elimination of conjugated metabolites. Their therapeutic value requires cautious use due to their potential for bleeding and pregnancy-related complications.

Anticancer compounds

Coumarin-based compounds display significant anticancer activity, acting through both growth-inhibiting (cytostatic) and cell-killing (cytotoxic) mechanisms. One of the early key findings in this area was reported by Weber et al. (1998), demonstrating that coumarin and its primary metabolite, 7-hydroxycoumarin, exhibit inhibitory effects against several human cancer cell lines. Even earlier research by Thornes and colleagues investigated the therapeutic potential of warfarin sodium-a well-known coumarin derivative-showing that it affected malignant V2 tumor cells as well as immune-related cells such as granulocytes, lymphocytes, and macrophages in experimental animals. Clinical studies have further supported the potential usefulness of coumarin derivatives in oncology.[34] Promising results have been documented in conditions such as metastatic renal cell carcinoma, prostate cancer, and malignant melanoma. Notably, the Irish Melanoma Study Group reported that daily oral administration of 50 mg of coumarin or warfarin significantly reduced the likelihood of recurrence in patients at high risk for malignant melanoma, and importantly, this dosage did not produce harmful side effects (Thornes et al., 1994). These observations suggest that coumarins may serve as preventive and therapeutic agents in certain cancer types.

Several mechanisms have been proposed to explain the anticancer effects of coumarin derivatives. For instance, 4-hydroxycoumarin was shown to decrease tyrosine phosphorylation levels in B16-F10 melanoma cells, thereby interrupting cellular signaling pathways critical for tumor progression. Meanwhile, 7-hydroxycoumarin has been found to inhibit myosin light chain kinase, interfering with cellular contractility and movement. Additionally, some coumarin derivatives disrupt the normal formation and functioning of the mitotic spindle during cell division. This interference leads to improper chromosome alignment and segregation, ultimately resulting in mitotic arrest and cell death. Overall, coumarin derivatives represent an important class of bioactive molecules with diverse anticancer mechanisms and strong potential for further therapeutic development.[35]

Anticancer Perspectives

Coumarin and its various derivatives have emerged as promising therapeutic agents in modern anticancer research. These substances have shown promise in treating a number of cancers, including those of the blood (leukemia), skin (malignant melanoma), prostate, breast, lungs, and colon. The core structure of coumarin consists of a benzene ring fused with a α-pyrone ring, creating a chemical backbone that is highly adaptable for structural modifications. This intrinsic versatility allows scientists to develop numerous derivatives with improved anticancer activity and reduced side effects.[36]

One of the most significant attributes of coumarins is their capability to regulate key biochemical pathways involved in cancer cell survival and proliferation. Their anticancer action is predominantly linked to the induction of apoptosis, also known as programmed cell death.[37] Additionally, certain coumarin chemicals inhibit the growth of cancer cells by interfering with tubulin, a protein necessary for cell division. Additionally, certain coumarins inhibit carbonic anhydrase enzymes, which are often overexpressed in tumor cells to help them adapt to acidic microenvironmental conditions. By blocking these enzymes, coumarins disrupt cancer cell metabolism and reduce their ability to invade surrounding tissues.[38] To further improve their therapeutic performance, scientists have designed hybrid molecules, such as coumarin-azole combinations, which exhibit superior anticancer potency and selectivity.[39] These chemical modifications enhance characteristics such as membrane permeability, metabolic stability, and target specificity. Currently, conventional cancer treatments like chemotherapy and radiation often come with severe side effects and may not effectively prevent cancer recurrence. Coumarins have special properties in biological systems because of their multi-targeted actions, natural origin, and general tolerability.[40]

Colon Cancer

Colon cancer remains one of the most serious global health challenges and is recognized as one of the leading causes of cancer-related death. In 2018, approximately 1.8 million new cases were diagnosed, and around 881,000 individuals died from the disease, placing colon cancer as the second most fatal malignancy worldwide.[41] Early detection plays a critical role in patient survival. When identified at an early stage, survival rates can reach up to 90%. However, in advanced or metastatic stages, survival rates fall drastically to nearly 10%, highlighting the urgent need for improved screening methods and more effective therapeutic strategies. The development and progression of colon cancer involve multiple genetic and molecular alterations, making treatment complex. Due to limitations in current therapies, researchers have turned their focus toward natural and synthetic compounds with anticancer properties. Coumarin derivatives, in particular, have gained considerable interest. Osthol, a natural coumarin derivative, has demonstrated selective cytotoxicity against colon cancer cells with minimal damage to normal cells. Studies indicate that osthol may disrupt key signaling pathways involved in cancer cell proliferation and survival, thereby suppressing tumor growth.[42]

Additionally, modified forms of coumarin have shown enhanced anticancer activity. Dicoumarol, another derivative, has been found to trigger programmed cell death (apoptosis) in colon cancer cells that overexpress the HMGA2 protein, a marker linked to aggressive tumor behavior. Dicoumarol has also exhibited synergistic effects when combined with 5-fluorouracil (5-FU), a standard chemotherapeutic drug used in colon cancer treatment. This combination may improve therapeutic outcomes while potentially lowering the required drug dosage and reducing associated side effects. A major obstacle in treating colon cancer is the presence of KRAS mutations, which often lead to resistance against targeted therapies. Coumarin-based compounds are advantageous in this context because they can act through multiple cellular pathways, offering treatment possibilities even in resistant cases.[42] Certain newly developed coumarin analogs have shown strong cytotoxicity against KRAS-mutated cancer cells, making them promising candidates for further drug development. Alongside coumarin derivatives, curcumin, the principal active compound in turmeric, has demonstrated significant anticancer potential in colon cancer. Curcumin can inhibit tumor growth by blocking inflammatory and proliferative signaling pathways such as NF-κB and PI3K/Akt.[39] It also promotes apoptosis by increasing pro-apoptotic proteins (Bax, p53) and decreasing anti-apoptotic proteins (Bcl-2). Moreover, curcumin may reduce metastasis and improve the effectiveness of conventional chemotherapeutic drugs like 5-FU.[43]

Stomach Cancer

Stomach cancer, also referred to as gastric cancer, continues to be a significant medical concern worldwide. The occurrence of stomach cancer is influenced by a variety of risk factors.[44] Environmental and lifestyle factors also play a critical role. Chronic infection with Helicobacter pylori is recognized as one of the strongest risk factors due to its role in long-term gastric inflammation.[45] Additionally, smoking, diets high in salted or smoked foods, low intake of fresh fruits and vegetables, and alcohol consumption contribute to disease development. Due to the often asymptomatic nature of early-stage gastric cancer, many cases are diagnosed at advanced stages where treatment options are limited and survival rates are low. Thus, there is ongoing scientific interest in finding new therapeutic compounds that can effectively inhibit tumor growth and induce cancer cell death.[46]

Among the natural product-derived compounds under investigation, coumarin derivatives have shown promising therapeutic potential. One such compound, styrene-substituted biscoumarin (SSBC), has been studied for its effects on human stomach cancer cell lines, particularly AGS cells.[47] Laboratory studies, including MTT cytotoxicity assays, suggest that SSBC can significantly reduce cancer cell viability. Molecular docking studies further reveal that SSBC can bind to key anti-apoptotic proteins, which normally function to prevent programmed cell death. By interfering with these proteins, SSBC appears to activate intrinsic apoptotic pathways, leading to controlled cell destruction and suppression of tumor proliferation. These findings indicate that SSBC could serve as an effective agent for promoting apoptosis-mediated cancer cell inhibition. In addition to coumarin derivatives, curcumin, a natural polyphenolic compound extracted from the rhizome of Curcuma longa (turmeric), has gained considerable attention for its anticancer potential. Curcumin exhibits strong anti-inflammatory, antioxidant, and antiproliferative properties. In gastric cancer cells, it has been shown to downregulate critical signaling pathways such as NF-κB and PI3K/Akt, which play essential roles in cell growth, invasion, and resistance to therapy.[43] Curcumin also increases the levels of pro-apoptotic proteins like Bax while decreasing anti-apoptotic proteins such as Bcl-2, thereby enhancing the induction of apoptosis. Additionally, curcumin may help reduce metastasis and limit cancer stem cell activity, contributing to long-term treatment success. Together, SSBC and curcumin represent promising therapeutic candidates in gastric cancer. By modulating vital cellular pathways and promoting apoptosis, these compounds may help improve future treatment strategies and patient outcomes.[48]

Future perspectives

The continuous rise in global cancer incidence and mortality emphasizes the need for more effective strategies in early detection, prevention, and therapeutic

intervention. Despite remarkable progress in oncology, current treatment options such as chemotherapy, radiotherapy, and targeted therapies are frequently associated with limitations including drug resistance, systemic toxicity, and non-selective mechanisms of action.[49] Therefore, there is a strong and ongoing demand for compounds that can selectively target cancer cells while minimizing adverse effects. Coumarin and its derivatives have emerged as promising scaffolds in the development of new anticancer agents due to their diverse pharmacological properties, structural versatility, and ability to modulate various biological pathways.[50] In recent years, extensive research has focused on evaluating coumarin-based derivatives for their anticancer potential using both natural and synthetic approaches. Natural sources, including medicinal plants, have yielded a wide range of coumarin analogues with notable cytotoxic, pro-apoptotic, and antiproliferative activities. The incorporation of coumarin into hybrid molecular structures has further expanded their therapeutic potential.[51] For example, the conjugation of coumarin with steroids, heterocyclic rings, or other bioactive fragments has produced derivatives with enhanced cellular permeability, improved target affinity, and reduced toxicity. These hybrid molecules demonstrate the capacity to interact with multiple cellular pathways simultaneously, which may help to overcome multidrug resistance-a major barrier in cancer therapy.[52] Synthetic chemistry has also played a crucial role in advancing coumarin research. Techniques such as multi-component reactions, ultrasound-assisted synthesis, and microwave irradiation have significantly improved the efficiency of coumarin derivative production by reducing reaction time, increasing product yield, and minimizing chemical waste. These methods align with green chemistry principles and enable rapid generation of diverse coumarin libraries for biological screening.[53]

Mechanistic studies have shown that coumarin derivatives exert anticancer effects through multiple modes of action. These include induction of apoptosis, inhibition of angiogenesis, suppression of cell proliferation, interference with DNA replication processes, and disruption of oxidative stress pathways.[54] Recent investigations into coumarin–azole derivatives suggest that their interaction with DNA or topoisomerase enzymes can induce DNA fragmentation and cell cycle arrest, particularly in rapidly dividing cancer cells. Moreover, several coumarin-based compounds have demonstrated the ability to modulate reactive oxygen species (ROS) levels and influence mitochondrial pathways, offering an additional mechanism for selective cancer cell death. Combination therapy also represents a promising direction for the future use of coumarins in oncology. This comprehensive strategy may improve treatment results, especially for cancer that is resistant.[55] Comprehensive in vivo studies and clinical trials are required to validate the pharmacokinetics, bioavailability, toxicity profiles, and long-term safety of coumarin derivatives.[56] Structural optimization through computational drug design and molecular docking can further refine coumarin analogues to achieve increased selectivity for cancer biomarkers.[57] As more coumarin derivatives progress through preclinical evaluation and into clinical investigation, there is growing optimism that novel coumarin-inspired molecules will soon provide safer and more targeted treatment strategies for patients with diverse malignancies. Ultimately, the continuing advancement of coumarin research holds significant promise to support the broader goals of modern oncology-improving patient survival, reducing treatment-associated morbidity, and enhancing overall quality of life.[58]

Toxicology

Coumarin was categorized as a toxic compound by the U.S. Food and Drug Administration (FDA) in 1954 after studies revealed its potential to induce liver tumors in rats. As a result, the use of coumarin as a flavoring agent in food products was prohibited.[59] Similarly, the National Institute for Occupational Safety and Health (NIOSH) identified coumarin as a potential carcinogenic substance, primarily based on rodent-based experimental findings. Despite this classification, it is important to emphasize that coumarin has not consistently shown mutagenic behavior in various genotoxicity assays, indicating that its carcinogenicity may not be directly linked to DNA damage.[40] The toxic and carcinogenic responses to coumarin are known to be highly species-specific. Experimental data demonstrate that certain animals, such as rats and mice, are more susceptible to liver toxicity caused by coumarin exposure, leading to hepatic injury or tumor formation. However, these effects are not uniformly observed across all species. This inter-species variation is largely associated with differences in metabolic pathways that govern coumarin biotransformation.[60] In humans, resistance to coumarin-induced liver damage is linked to the predominance of the coumarin 7-hydroxylation metabolic pathway. This pathway effectively converts coumarin into a less toxic metabolite, thereby preventing the accumulation of harmful intermediate compounds.[56] Individuals with reduced activity of this metabolic route may theoretically be at a slightly increased risk of toxicity. Overall, although coumarin demonstrates hepatotoxic and carcinogenic potential in specific laboratory animals, these findings cannot be directly generalized to humans due to major metabolic and physiological differences.[61]

CONCLUSION

Coumarin and its derivatives have emerged as promising therapeutic molecules due to their broad spectrum of anticancer activities and favorable pharmacological profiles. Their chemical framework allows interaction with multiple cellular targets, leading to the induction of programmed cell death, suppression of tumor cell growth, interference with metastatic signaling, and disruption of essential proteins such as tubulin. Compounds including osthol, dicoumarol, and

biscoumarins have shown notable selectivity toward cancer cells, which may help reduce adverse effects commonly associated with conventional chemotherapy. Their ability to act synergistically with standard anticancer agents, such as 5-fluorouracil, suggests potential for enhancing treatment efficacy while lowering drug dosage requirements.

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