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A Comprehensive Study on Synthesis of Coumarins and Coumarin Related Compounds in Pharmacotherapy of Cancer

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Abstract: *Cancer is one of the most common causes of disease-related deaths worldwide. Despite the discovery of many chemotherapeutic drugs that inhibit uncontrolled cell division processes for the treatment of various cancers, serious side effects of these drugs are a crucial disadvantage. In recent years, researchers have focused on the anticancer activity coumarins, due to their high biological activity and low toxicity. Coumarins are commonly used in the treatment of prostate cancer, renal cell carcinoma and leukemia, and they also have the ability to counteract the side effects caused by radiotherapy. In this review, a compilation of various research reports on coumarins with anticancer activity and investigation and a review of structure-activity relationship studies on coumarin core are presented. Determination of important structural features around the coumarin core may help researchers to design and develop new analogues with a strong anticancer effect and reduce the potential side effects of existing therapeutics.*
The structural motif of coumarins is related with various biological activities and pharmacological properties. Both natural coumarin extracted from various plants or a new coumarin derivative synthesized by modification of the basic structure of coumarin, in vitro experiments showed that coumarins are a promising class of anti-tumor agents with high selectivity. Cancer is a complex and multifaceted group of diseases characterized by the uncontrolled and abnormal growth of cells in the body. This review focuses on the anticancer mechanism of various coumarins synthesized and isolated in more than a decade. Isopentenyloxycoumarins inhibit angiogenesis by reducing CCl2 chemokine levels..

Keywords: Benzopyrone; Coumarin; Cancer; Drug Discovery; Natural Product..

I. INTRODUCTION

Coumarins are polyphenolic compounds belonging a group of colorless and crystalline oxygenated heterocyclic compounds first isolated from the plant named Dipteryx odorata Willd. (Fabaceae) known locally as “coumaroun” by Vogel in 1820 [1]. Oxygenated heterocyclic compounds are furan derivatives with 4C atoms or pyran derivatives with 5C atoms. Although furan derivatives are rarely present in plants, pyran derivatives forming the structure of various compounds are encountered more frequently. The pyran derivatives are ketonic compounds that in the form of α-pyron or γ-pyron. Secondary metabolites called benzo- α-pyrone (coumarin) and benzo-γ-pyrone (chromone) occur due to condensation of pyron derivatives with benzene in plants [2]. Coumarin (1,2-benzopyrone or 2H-1-benzopyran-2-one) and coumarin derivatives are natural compounds that are widely available in plants as a heteroside or free form. A total of 800 coumarin derivative compounds that naturally found were obtained from about 600 genera of 100 families to date [3]. Coumarin and its derivatives are frequently found in the seeds, roots and leaves of many plant species belonging to families (especially Rutaceae and Apiaceae) in the Dicotyledonae class of the division of Spermatophyta. Although most natural coumarins are isolated from vascular plants, some coumarins such as novobiocin, coumermycin and aflatoxin are isolated from microbial sources [4]. These compounds have become of importance in recent years due to their various biological activities. Previous biological activity studies performed on coumarin derivatives revealed that these compounds have antitumor [5]. photochemotherapy, anti-HIV [6], antibacterial and antifungal [7], anti-inflammatory [8], anticoagulant [inhibitors of the enzyme VKOR (vitamin K epoxide reductase)] [9], triglycerides lowering [10] and central nervous system stimulant effects [11]. However, a strong antioxidant and protective effect

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against oxidative stress by scavenging the reactive oxygen species has also been reported for hydroxycoumarins [12]. In addition, the discovery of coumarins with weak estrogenic activity has enabled the usage of this type of coumarins in the prevention of menopausal distress [13]. On the other hand, the usage of some coumarin derivatives as a tobacco flavor, which are used as fixative and flavoring agents, has been regulated by the FDA because of its negative effects, such as mild nausea, diarrhea and hepatotoxicity [14]. Besides their medical use, coumarins are also used in the cosmetic industry and agrochemical industry, as well as optical brightening agents [15].Both natural and synthetic coumarin derivatives draw attention due to their photochemotherapy and therapeutic applications in cancer [16].It has been reported that substitution patterns can affect the therapeutic, pharmacological and biochemical properties of coumarins in a positive way [17].For instance, the substitution of a methoxy group at the 7-position and a 3-methyl 2-butenyl group at the 8-position of the osthol leads to a strong reduction of plasma alkaline transferase (ALT) level in hepatitis and inhibition of caspase-3 activation [18].Some coumarins have cytostatic effect, while others have cytotoxic activity [19].It has been revealed to show cytostatic activity of coumarin and its active metabolite, 7- hydroxycoumarin, on human cancer cell lines such as HL-60 (leukemia), MCF-7 (breast), A549 and H727 (lung) and ACHN (kidney). Moreover, cytostatic activity of these compounds against prostate cancer, malignant melanoma and metastatic kidney cell carcinoma has also been reported in clinical studies [20]. Compounds of 3 and 4-hydroxycoumarin structure were determined to inhibit cell proliferation in the gastric carcinoma cell line [21].In vitro proliferation analysis investigating the mechanism of action of coumarins on the growth and metabolism of MCF-7 and A549 human tumor cells revealed that coumarin was not responsible for observed in vivo effects, but was a precursor of other active metabolites [22]. Previous studies showed that ortho- or meta-dihydroxycoumarins have more cytotoxic effect on human tumor cell lines than mono-hydroxycoumarins [23]. In the current review, compilation of various research reports on natural and synthetic coumarin derivatives with anticancer activity and investigation and review of structure–activity relationship studies on coumarin core were aimed. Determination of important structural features around the coumarin core may help researchers to design and develop new analogues with a strong anticancer effect and reduce the potential side effects of existing therapeutics.

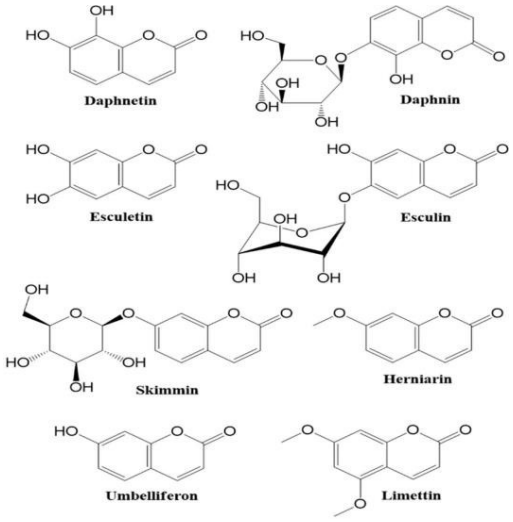

Figure 1:- Chemical structures of some simple coumarins.

1.1 Occurrence:-

Coumarins are classified in four groups: simple coumarins, furanocoumarines, pyranocoumarins and pyrone-substituted coumarins [24]. Simple coumarins: these are composed of hydroxylated, alkoxylated and alkylated derivatives of coumarin and their glycosides (e.g., Umbelliferone, skimmin, limettin, herniarin, esculetin, esculin, daphnetin and daphnin (Figure 1)) [24].

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Figure 1:- Chemical structures of some simple coumarins. Furanocoumarins: This group of coumarins consists of a furan ring fused with a coumarin. They are divided into two groups as C6/C7 (linear) type, C7/C8 (angular) type according to the attachment place of the furan ring. (e.g., psoralen, xanthotoxin, bergapten, imperatorin, isopimpinellin, anjelisin, isobergapten and pimpinellin [25].

Chemical structures of some furanocoumarins. Pyranocoumarins: six-membered pyran ring is fused with the benzene ring via C6-7 (linear) or C7–8 (angular) (e.g., visnadin, xanthyletin and seselin) Pyrone-substituted coumarins: These are classified in three groups: 4-Hydroxycoumarin (Novobiocin and Dicumarol), 3-Phenylcoumarin (Coumestroln and Gravelliferone) and 3,4- Benzocoumarin (Aeternaryiol). 4- Hydroxycoumarins are not found in plants in free form. Warfarin, a synthetic compound, belongs to this group [26].

Multi-target compounds are recently being searched for and these compounds are thought to be promising compounds for the treatment of several disorders, including cancer and heart failure. In this context, compounds observed from natural sources come into prominence due to their low toxicity, low drug resistance, low cost and high efficacy [27]. Therefore, new compounds isolated from natural sources, such as plants and animals, and possible combination of these compounds with conventional chemotherapeutic agents seems to be important strategies to improve life quality, especially in cancer patients [28]. Coumarin-based structure compounds constitute a major group of natural compounds with various pharmacological effects. These group of compounds can be isolated from different plants, including Achillea, Artemisia and Fraxinus genera, and also, they can be synthesized through various chemical reactions. Several strategies such as maceration, reflux, ultrasonic- assisted and microwave extraction methods are used for the isolation and purification of coumarin compounds. Perkin, Von Pechmann, Knoevenagel and Wittig organic reactions are some of reactions that coumarins can be synthesized [29]. In the biosynthetic origin of coumarins, the shikimic acid pathway plays an important role. In this pathway, there are several enzymatic steps leading to occur chorismic acid, cinnamic acid, p-coumaric acid and umbelliferone. Moreover, the cytochrome P450 enzymes have a crucial role in the ortho-hydroxylation of cinnamic acid leading to occur umbelliferone, scopoletin and isofraxidin [30].

II. LITERATURE REVIEW

2.1 Cancer Treatment

Although some standards have been determined for cancer therapy, various approaches and treatments are applied for specific to each type of cancer. Biological therapies, such as radiotherapy, chemotherapy, surgery, immunotherapy, hormone therapy, targeted therapies and gene therapy can be used alone or in combination in cancer therapy. However, these methods, known as the gold standard, have advantages as well as disadvantages. Despite the discovery of many chemotherapeutic drugs (Adriamycin, Cisplatin, Campotins, Vinblastin, Mercaptopurine, etc.) that inhibit uncontrolled cell division process for the treatment of different types of cancer , serious side effects of these drugs on hematopoietic system, bone marrow and gastrointestinal epithelial cells and hair follicles are a crucial disadvantage .In addition, multi-drug resistance (MDR) is another important problem in anticancer treatment. Due to problems such as cytotoxicity and drug resistance in existing chemotherapeutic agents, many investigations are being conducted to discover and develop effective anticancer drugs. Previous studies showed that many compounds obtained from natural resources can be used as preventive and therapeutic agents in cancer therapy.

2.2 Roles of Coumarins in Anticancer Activity

Studies conducted on the anticancer activity of coumarin and its derivatives revealed that the mechanism of action of these compounds is generally caspase dependent apoptosis.CYP 2A6, an isoform of cytochrome P450, metabolizes coumarin to 7-hydroxycoumarin, which has an antiproliferative effect by reducing Bcl expression in various organs and tissues. Bcl-2, a 26 kDa membrane protein, blocks free oxygen radicals, inhibits mitochondrial CYP and suppresses activation of caspase-9, which extends the cell life cycle cumulatively. Thus, it causes carcinogenesis and leads to accumulation of oncogenic mutations in the normal cell. Caspase-9 is activated by Bax, a membrane protein. Over-expression of Bax causes mitochondrial cytochrome C to be released into the cytoplasm through modulation in the mitochondrial membrane. Cytochrome C in the cytoplasm activates caspase-9 and activation of caspase-9 leads to the caspase-3, 6 and 7 activation which breaks down key cytoplasmic and nuclear proteins. Coumarins regulate the fate of

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normal cells by modulating signal transduction pathways containing GTP-binding proteins and reducing Bcl-2 expression. The Bcl-2 protein family consists of Group 1 (Bcl-2 and Bcl-XL), which are apoptotic, and Group 2 (Bax, Bad, Bid and Bak), which are pro-apoptotic. BH1, BH2 and BH3 in the Bcl-2 protein family and their dimerization determine the sensitivity of a cell to negative stimuli. As the ERK/MAPK pathway actively participates in cell proliferation and cytokine production, this pathway is used as an important target for the development of new anticancer agents.

2.3 Coumarins in Breast Cancer

The breast tissue is composed of lobules formed by the glands that produce milk, ducts that allow milk to be discharged and fat and connective tissues. Lobes are formed by combination of the lobules, and each breast has 15–20 lobes. The lobules are connected to each other by milk ducts and milk ducts join towards the nipple. The development and physiological functions of the breast are regulated by hormones. The main hormones that provide the development of breast tissue are estrogen and progesterone.

Breast cancer is a systemic disease that occurs when the cells lining the mammary glands and milk ducts proliferate abnormally, spread to various tissues and organs and continue to grow there. It is a complex disease that affects women physically, psychologically and socially [89], and ranks first among cancer types seen in women in the world, and also second most common cause of death due to cancer following the lung cancer. In epidemiological studies, the prevalence was found to be 22–26% and the risk of breast cancer-related mortality was around 18%. Since the breast consists of two main structures, there are two types of breast cancer: lobular cancer developing from the milk secreting part and ductal cancer developing from the milk ducts. The most common type of breast cancer is ductal cancer and accounts for 75% of all breast cancers. Breast cancers are histologically divided into two main groups, in situ and invasive carcinomas.

2.4 Coumarins in Leukemia

Leukemia is a clonal disease that results from neoplastic exchange of hematopoietic precursor cells in the bone marrow. Marrow damage occurs when a large number of immature and malignant cells replace normal marrow cells. Thus, decrease begins in the number of platelets involved in blood coagulation and the number of leukocytes involved in defense. This causes intense injuries and bleeding in patients with leukemia, as well as easy infection. Moreover, the defense mechanism weakens and may cause anemia and shortness of breath in advanced stages. Leukemia has symptoms such as weakness and fatigue, fever, some neurological symptoms, bloating and bleeding in the gums.

Leukemia is a type of cancer which effects the blood production system (lymphatic system and bone marrow) in the body. Leukemia is classified as acute or chronic (they are subdivided according to their appearance under the microscope) and according to the spread and development characteristics of the tumor. Generally, acute leukemia occurs in children, while chronic leukemia tends to be more common in adults. There are different types of blood cancers according to the cell type (such as myeloid and lymphoid) and the duration of the disease. Some types of blood cancers show a faster and poor prognosis. Leukemia is more common in childhood than other types of cancers, and 30–35% of cancers in this period are composed of leukemia. Frequency is 3–4 in 100,000 in children under 15 years of age in western countries. Although the causes are not known exactly, both genetic and environmental factors are thought to play an important role in leukemia. Mutations in DNA in somatic cells cause activation of oncogenes or inactivation of tumor suppressor genes. Thus, regulation of cell death and division is damaged. Apart from genetic reasons, this damage is thought to be caused by petrochemicals, radiation, carcinogens and some viruses (e.g., HIV).

2.5 Coumarins in Renal Cell Carcinoma

Renal cell carcinoma (RCC) is responsible for approximately 3% of tumors seen in adulthood. In recent years, especially with the widespread use of imaging methods, there is an increase in the incidence of RCC at every stage and mortality rates resulting from disease. One third of patients with RCC are metastatic at the time of diagnosis, or one third of them develop metastases despite treatment. Most of the tumors in RCC are associated with large, locally advanced and often lymph node, renal vein or vena cava invasion, and histologically, approximately 90% are

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transparent cell types. Metastasis occurs in many organs, especially lung, liver, bone, adrenals, pancreas, brain, thyroid gland, skin and ureter in order of frequency. While the transparent cell type metastasizes to the lungs more often, papillary type makes it to the lymph nodes and the chromophobes to the liver .The average survival in these patients is 10–12 months, and the 2-year survival rate is 18–20%.

There have been promising developments in prognosis with the introduction of new molecules that make up immunotherapy and targeted therapy, a better understanding of the timing and effectiveness of cytoreductive nephrectomy, and the use of these methods together. Response rates do not exceed 10–15% in immunotherapy using IL-2 and interferon alfa.

2.6 Coumarins in Prostate Cancer

Prostate cancer is the most common solid tissue cancer that occurs with the uncontrolled growth of cells in the prostate gland. Cancer cells primarily grow uncontrolled and spread into the prostate. These then reach the capsule surrounding the prostate, pierces the capsule and spreads out of the prostate. Unlike benign prostate gland enlargement, prostate cancer does not originate from the center of the prostate, but from its decentralized, distal center. Therefore, urinary complaints in prostate cancer disturb the patient in the later period. It is characterized by a very slow growth rate and broad biological variability in terms of hormonal sensitivity. It can spread to nearby organs, the lymphatic system and other parts of the body through the bloodstream during the period of growth and spread. Prostate cancer has a slow course, but the tumor may show a rather aggressive character and spread to the bones and other organs. According to the data of American Cancer Society, men have been reported to have 16.7% risk of development of prostate cancer life-long, and a 2.5% risk of life loss. One in every 5–6 men is at risk of developing prostate cancer throughout their life. When prostate cancer is diagnosed at an early stage, it is among the cancer types with high treatment success.

III. FUTURE SCOPE

The future of coumarin and coumarin-related compound synthesis for cancer pharmacotherapy is promising, given the increasing interest in developing targeted, effective, and less toxic cancer treatments. While traditional chemotherapies have made significant strides, their side effects, resistance development, and limited efficacy in treating advanced cancers underline the need for novel compounds like coumarins. The ongoing research into their synthesis, mechanism of action, and potential clinical applications is likely to expand the therapeutic utility of coumarin derivatives in several exciting ways. Below are key areas where future progress is expected:

3.1 Design and Synthesis of Targeted Coumarin-Based Anticancer Agents

One of the most promising areas of research is the development of targeted anticancer therapies that selectively attack cancer cells while minimizing damage to normal tissues. Coumarins, due to their bioactivity, are prime candidates for further modification to enhance their specificity toward cancer cells.

Targeted Drug Delivery: Conjugating coumarin derivatives with targeting ligands (such as antibodies, peptides, or aptamers) could allow the selective delivery of the drug to cancer cells. This approach may improve therapeutic efficacy and reduce off-target toxicity.

Coumarin-Drug Conjugates: Combining coumarin derivatives with established chemotherapeutic agents (e.g., doxorubicin, paclitaxel) can lead to synergistic effects. These hybrid compounds could work through multiple mechanisms, such as inhibiting cancer cell proliferation while also inducing apoptosis.

Nanomedicine: Encapsulating coumarin derivatives in nanoparticles (such as liposomes, micelles, or dendrimers) offers improved bioavailability, prolonged circulation time, and targeted release of the drug to the tumor site. Nanocarriers also protect sensitive coumarins from degradation, improving their stability.

3.2 Development of Multi-Functional Coumarin Derivatives

A future direction will be to create multi-functional coumarin derivatives that can target multiple pathways involved in cancer progression. These compounds could have a broader spectrum of action against cancer cells and may help overcome drug resistance.

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Combination Therapy: Coumarins with multiple pharmacological properties, such as anti-inflammatory, anti-angiogenic, and anti-metastatic activity, can be designed. For example, coumarin derivatives that target both cancer cell proliferation and angiogenesis (blood vessel formation) could limit tumor growth and spread.
Cancer Stem Cells: Recent studies suggest that cancer stem cells (CSCs) contribute to tumor recurrence and resistance to therapy. Coumarins can be engineered to selectively target CSCs, inhibiting their self-renewal properties and preventing relapse.

3.3 Coumarin Derivatives for Overcoming Chemoresistance

Cancer cells can develop resistance to chemotherapy by various mechanisms, including the upregulation of efflux pumps (such as P- glycoprotein), alteration of drug targets, and changes in the tumor microenvironment. Coumarin derivatives could be explored to overcome these resistance mechanisms.
Inhibition of Drug Efflux Pumps: By designing coumarin-based compounds that inhibit P-glycoprotein or other ABC transporters, researchers could enhance the intracellular concentration of chemotherapy drugs, restoring their effectiveness in resistant tumors.
Combination with Epigenetic Modulators: Coumarins could be combined with epigenetic modulators to reverse drug resistance. By inhibiting enzymes involved in DNA methylation or histone modification, these compounds may re-sensitize resistant cancer cells to chemotherapy.

3.4 Fluorescent Coumarin Derivatives for Cancer Diagnosis and Monitoring

Fluorescent coumarin derivatives are emerging as excellent candidates for in vivo cancer imaging and monitoring of treatment efficacy. The non-invasive nature of fluorescence imaging makes it ideal for tracking the progression of cancer and the pharmacokinetics of drug delivery systems.
In Vivo Imaging: Researchers are working on designing coumarin-based probes that can be used for fluorescence imaging in preclinical models and eventually in human patients. These probes can enable real-time monitoring of tumors and allow physicians to observe drug delivery and release kinetics.
Cancer Cell Detection: Fluorescent coumarins could be further optimized to selectively bind to cancer cell markers or metabolic changes that occur specifically in tumors. This selective targeting may enhance the accuracy of early cancer detection.

IV. CONCLUSION

The widespread distribution and various bioactivity of coumarins have led scientists to carry out research involving this ring system for decades. Coumarins have many biological activities, including disease prevention, growth modulation and antioxidant properties. It has been shown in scientific studies that these compounds show antitumor effects depending on their effects on immune regulation, cell growth and differentiation. It is extremely important to identify new, effective and less side effect anticancer products based on traditional medicines. Synthesis of coumarin and its derivatives is possible thanks to a number of innovative techniques, including the Pechmann, Claisen, Perkin, Knoevenagel and Wittig reactions. Although there are important limitations in use of most natural coumarins due to their hepatotoxic effect, relatively safe analogues with higher potency and thus better therapeutic index have been obtained by molecular manipulations. In the structure–activity studies on coumarins, significant positive results were obtained in anticancer activity screening with the addition of substituents at different positions of the coumarin core. Therefore, the development of new anticancer molecules by attaching appropriate functional groups to different positions around the coumarin core is an important research area.
However, significantly positive results were obtained in anticancer effect studies for various cancer types by targeting natural and synthetic coumarins to specific signaling pathways. Coumarin and coumarin-derived compounds are a potential source of anti-cancer drugs that need further researches, and it is obvious that they will be an important group in the development of new anticancer drugs.
In conclusion, the synthesis of coumarins and their derivatives holds immense promise for the future of cancer treatment, offering novel strategies that may significantly improve patient outcomes. As research progresses, these

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compounds are poised to become an integral part of next-generation cancer therapies, providing more effective, targeted, and safe treatment options for patients battling this complex and multifaceted disease.

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