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Professional paper

A REVIEW OF COUMARIN DERIVATIVES IN PHARMACOTHERAPY

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Abstract

Coumarins are proven precursors in the synthesis of many medicinal compounds and the heterocycles derived from them are widely appreciated for their numerous pharmacological effects. Molecules containing coumarin rings have been studied for their antiviral, antimicrobial, antifungal, anti-inflammatory, anticonvulsant, anticoagulant, antipsychotic, and anticancer effects. Thus, the isolation, structural characterization, and pharmacological evaluation of new derivatives combining coumarin rings continuously provoke research interest. In this paper, a brief overview of the chemical, biopharmaceutical, pharmacokinetic, and pharmacological properties, as well as the structure-activity relationship for many coumarin derivatives, is given, with a special focus on new compounds as potential chemotherapeutics or key components for the synthesis of drugs intended for the treatment of cancer.

Keywords: coumarins, pharmacological effect, SAR, cancer

1. Introduction

Coumarins owe their class name to 'Coumarou', the vernacular name of the tonka bean (Dipteryx odorata Willd, Fabaceae), from which coumarin, it was isolated in 1820 (1). Coumarins have been known for a long time in therapy as anticoagulants, and drugs such as warfarin and similar compounds are widely used to prevent possible complications from pathological blood coagulation (2, 27). Coumarin and related compounds have been known for their multiple pharmacological effects based on the antioxidant effect and the modification of immune responses, cell growth, and differentiation (1,3). They and their derivatives are proven precursors for the synthesis of a range of medical compounds and the heterocycles derived from them are examined concerning their anti-viral (4), anti-inflammatory and antioxidant (5, 7), anticonvulsant (6), antibacterial (7, 10, 19, 20), antifungal (8, 9), anticancer (11-16), and antiallergic effects (17,18).

2. Chemical profile

Coumarin is a member of the benzopyrone-α-family of compounds, which structurally includes four groups of coumarins: simple coumarins, furanocoumarins, pyranocoumarins, and pyrone-substituted coumarins (biscoumarins, tricoumarins, and coumarin ligands). Furanocoumarins consist of a five-membered furan ring attached to a coumarin core, while pyranocoumarins are analogs of furanocoumarins but contain a six-membered ring (Figure 1). Simple coumarins are hydroxylated, alkoxylated and alkylated derivatives of the parent compound, coumarin, together with their glycosides (21).

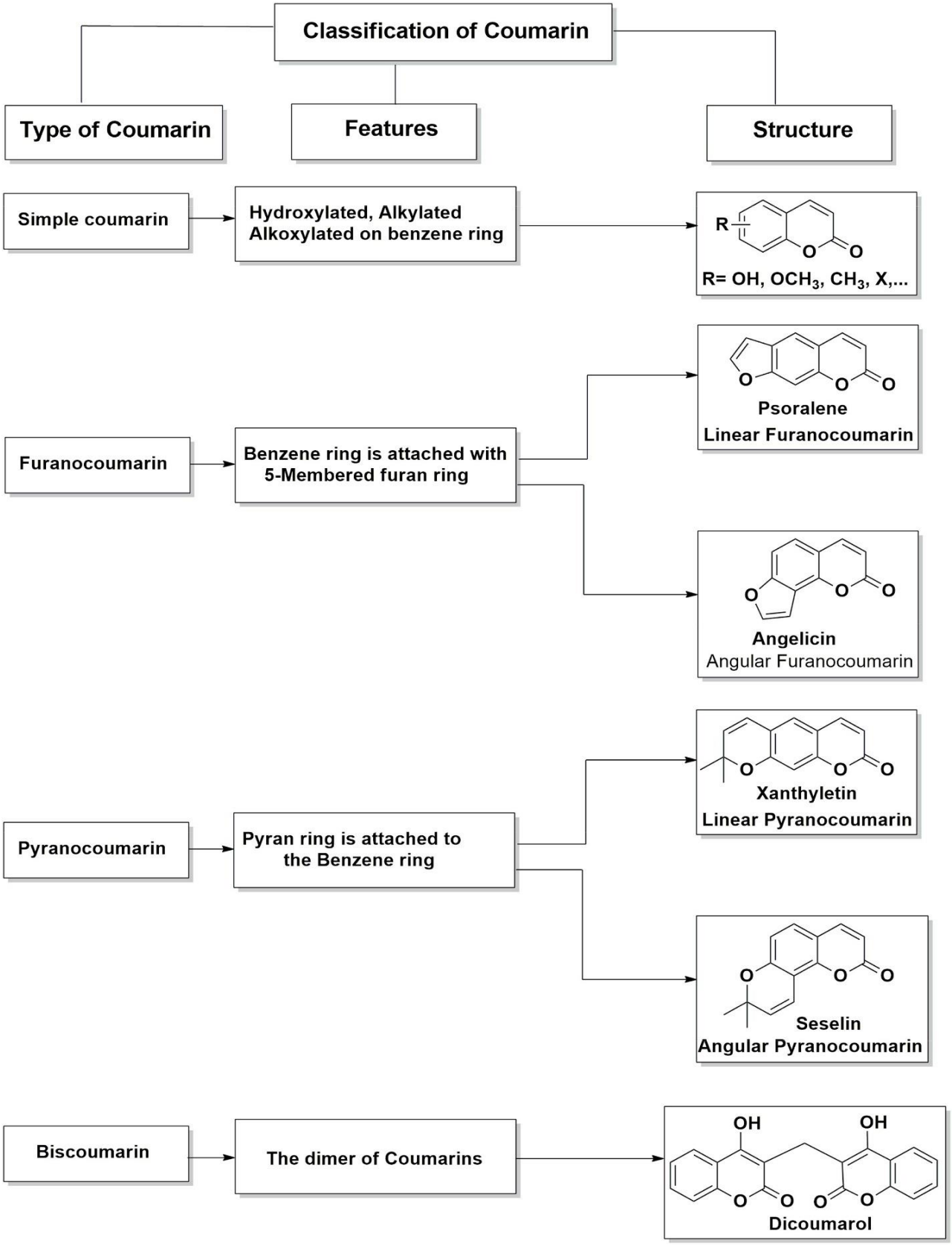

Figure 1. Classification of coumarin based on its type, feature and structures (21)

4-Hydroxycoumarin (4-HC) is part of the group of coumarins substituted in the pyrone ring (22,23). Coumarin is insoluble in water; however, the 4-hydroxy substitution leads to slightly acidic properties of the molecule, making it soluble in water under slightly alkaline conditions. Based on its structural simplicity, coumarin has been designated as the leading compound of the benzo-α-pyrones. It is generally accepted that 7-hydroxycoumarin is the parent molecule of the more complex coumarins.
Coumarin derivatives can be synthesized by one of the following methods: (i) Claisen rearrangement; (ii) Perkin reaction (formation of coumarin via aldol condensation of aromatic ortho-hydroxybenzaldehyde and acid anhydrides in the presence of an alkali salt of the acid); (iii) Pechmann reaction (condensation of phenols with β-ketoesters in the presence of acidic catalysts); (iv) Witting reaction (alkene formation from carbonyl compounds and phosphonium ions); (v) Knoevnagel condensation (condensation of aldehydes with active methylene compounds in the presence of ammonia or amines); (vi) Kostanecki-Robinson reaction (formation of 3- and 4-substituted coumarins, via acylation of ortho-hydroxyaryl ketones with aliphatic acid anhydrides, followed by cyclization), (vii) Reformatsky reaction (condensation of aldehydes or ketones with organozinc derivatives of α-haloesters to β-hydroxy esters) and other methods (24,25).

3. Pharmacodynamic profile, structure-activity relationship

Coumarins vary in their structure, which affects their biological activity (1). They are mainly oral anticoagulants, but this action is not characteristic of coumarin and 4-HC. The structure of bis-hydroxycoumarin refers to the minimum requirements for anticoagulant action, a 4-hydroxy group, a substituent in position 3 and a bis molecule, which is confirmed by comparative in vivo and in vitro studies of the anticoagulant effect of a series of 4-hydroxycoumarins with pyridine, pyrimidine and a pyrazole core linked at C-3 (26, 27).
The presence of phenolic, hydroxyl, and carboxyl groups in the coumarin structure is considered essential for antimicrobial and antifungal activity. The introduction of fluoro and sulfonamide substituents can improve biological activity (28).
Highly oxygenated coumarins with two methoxy functional groups and one additional phenolic group have shown the most promise to overcome the limitations of natural coumarin antibiotics, poor solubility, toxicity and resistance development, by inhibiting DNA gyrase (29, 30). A molecule with two planar systems and a p-nitro group was shown to be extremely active against the fungal cell wall, affecting cytochrome synthesis and inducing apoptosis (31). Phenprocoumon, warfarin, and substituted 4-hydroxy-2-pyrone derivatives are designated first-generation HIV-PR inhibitors. Certain coumarin dimers, especially with a hydrophobic linker component, have shown potent inhibitory activity against HIV-1 integrase (32). Other coumarin derivatives have been tested against Herpes simplex virus, with 5,7,4´-trihydroxy-4-styrylcoumarin proving extremely active in this context (33).
The anti-inflammatory effect of coumarins results from the inhibition of p38 MAP kinases and compounds containing pyrazolone and oxazolone are considered highly selective and potent inhibitors of these enzymes (34, 35). Substituents in coumarin at positions 4 and 7 contribute to high activity, and lipophilicity and degree of ionization have been shown to be extremely important, correlating with biological activity (36). Coumarins also inhibit certain enzymes (eg xanthine oxidase, monoamine oxidase (MAO), cholinesterase, 5α reductase, serine protease, carbonic anhydrase, etc.). The 7-hydroxycoumarin structure plays a significant role in the inhibition, but only of certain enzymes (eg xanthine oxidase), while the introduction of acetoxy/bromoallyloxy at position 7 results in higher MAO inhibition (37, 38, 39).
Inhibition of MAO A and B was also shown by coumarin derivatives that have a methoxy group in position 3, 4 or 5 in their structure (37, 40). Small changes in the substituents of the coumarin core contribute to the selectivity towards MAO A or MAO B enzymes (41).

Certain coumarins also possess anxiolytic, anticonvulsant, sedative and muscle relaxant effects (42, 43). An arylpiperazine fragment in the coumarin structure enhanced these effects by increasing the affinity for D2A, D3 and 5HT1A-receptors. Coumarins also block the enzyme acetylcholinesterase, a targeted therapy for Alzheimer's disease (44,45).

4. Biopharmaceutical and pharmacokinetic properties

Human pharmacokinetic studies have shown that coumarin is completely absorbed from the GI tract after oral administration and is extensively metabolized in the liver after the first pass; only 2-6% of the drug reaches the systemic circulation unchanged (46). Although coumarin can be metabolized by hydroxylation at six possible positions (C-3, 4, 5, 6, 7, and 8), hydroxylation most commonly occurs at positions 7 and 3. Hydroxylation of coumarin to 7-hydroxycoumarin is primarily mediated by CYP2A6. After 7-hydroxylation, coumarin undergoes glucuronidation. Hydroxylation of C-3 results in subsequent metabolism via ring opening and the formation of two products, o-hydroxyphenyl-lactic acid (o-HPLA) and o-hydroxyphenyl-acetic acid (o-HPAA) (46).

Both coumarin and 7-hydroxycoumarin are poorly soluble in water (0.22 and 0.03%, respectively). These percentages indicate theoretically low in vivo bioavailability, taking into account the fact that an aqueous solubility of 0.3% is considered the critical value at which the dissolution of the compound limits its rate of absorption. The low bioavailability of coumarin, in addition to its short half-life (1.0 h orally vs. 0.8 h intravenously), calls into question its importance in vivo, so today it is accepted that coumarin is a prodrug and 7-hydroxycoumarin is a therapeutic relevant compound. However, both compounds have high distribution coefficients, which is considered favorable for their rapid absorption once they are in aqueous solution. This, combined with the fact that coumarin is a non-polar molecule, suggests that coumarin can readily cross lipid bilayers by passive diffusion (47).

Literature data on coumarin permeability and substrate behavior towards P-glycoprotein (P-gp) are limited. Galkin et al. (48), evaluating the permeability of 18 coumarins with different numbers of OH, CH3 and OCH3 groups in Caco-2 colon cancer cell lines demonstrated high permeability of all tested coumarins and absorption not limited by efflux. All tested coumarins were more permeable apically to basolaterally. The type and position of the substituents had a greater influence on the permeability of the compounds than the number of substituents. Five coumarin derivatives affected the mitochondrial function of Caco-2 cells, but this effect had no effect on the permeability of the compounds.

Witgen et al. (49) sought to determine whether the efflux transporter proteins responsible for multidrug resistance (MRP1-4), the protein responsible for resistance to breast cancer and P-gp play a role in the transport of 7-HC and 7-HC-glucuronide (7-HC-G) in cancer cells. The results showed that 7-HC is not transported by any of the investigated efflux transporters, while 7-HC-G is a substrate of MRP3 and MRP4. These results are consistent with the pharmacokinetic profile of coumarin and indicate that MRP3 and MRP4 are the major transporters involved in the excretion of the coumarin metabolite 7 HC-G from the liver and kidney. Research by Wu et al. (50) reported marked synergistic activity when pyranocoumarins as P-gp inhibitors were combined with the common antitumor agents vincristine, Doxo and paclitaxel. Preliminary investigations of coumarin derivatives as new modulators of multiple resistance were also carried out by Kawase et al. (51), where among 44 coumarins, 14 showed moderate activity, while the most active compound, 6-hydroxy-3-(2-hydroxyethyl)-4-methyl-7-methoxycoumarin, was as potent as the modulator verapamil.

5. Coumarin derivatives in the treatment of cancer

A large number of authors in their studies and literature reviews highlight the importance of coumarin derivatives in the pharmacotherapy of various tumors, such as breast cancer (52, 53), leukemia (54), malignant melanoma (55), prostate cancer (56), lung cancer (57), metastatic kidney cancer (58) and others (52). However, despite numerous studies, little information is available regarding the cellular mechanism of action of coumarin compounds in the treatment of malignancies. Probably for this reason, they currently do not have a major role in the treatment of cancer. Hence, conducting thorough studies on the structure-activity relationship of coumarins, with special reference to carcinogenicity, mutagenicity and cancer prevention is of particular importance, considering that most coumarins may be useful in this aspect.

Several components of the signaling pathways stand out as potential mechanisms/cellular targets for the anti-tumor activity. Coumarin compounds can inhibit the growth, proliferation and metastasis of various tumor cells through a variety of mechanisms, including inhibition of carbonic anhydrase, PI3K/AKT/mTOR signaling pathway, microtubule polymerization, angiogenesis, monocarboxylate transporters, hypoxia-inducible factor-1; acting on apoptosis proteins and inhibiting tumor multidrug resistance, regulation ROS, and so on (59). Most of the drugs kill cancer cells by inducing apoptosis, which is the result of complex interactions between pro- and anti-apoptotic molecules that regulate homeostasis and eliminate damaged cells (60, 61). Depending on their structure, they act differently on different tumor cells; inhibit telomerase, protein kinase and down-regulate the expression of oncogenes or induce caspase-9-mediated apoptosis, suppress cancer cell proliferation, arrest the cell cycle in G0/G1 and G2/M phase, and affect P-gp on cancer cells (62, 63).

The different cytotoxic values of different coumarins are related to the presence and position of the hydroxyl groups; mainly, cytotoxic effects have been observed with ortho-dihydroxy substituents. All potentially active natural coumarins are thought to possess at least two phenolic groups at the 6,7 or 6,8 position. In addition, 5-formyl-6-hydroxy substituted semisynthetic analogues confirm the importance of at least two polar functions for high cytotoxicity, while the antimutagenicity of simple coumarins is associated with the presence of polar functions at C-3, -4 and -7 (64). The studies of certain hydroxylated and/or methoxylated coumarin derivatives regarding their relative cytotoxicity on human tumor cells (oral squamous cell carcinoma HSC-2 and HSC-3, melanoma A-375 and promyelocytic carcinoma HL-60) and normal cell lines (gingival fibroblasts HGF, periodontal ligament fibroblasts HPLF and pulp cells HPC) suggest tumor-specific cytotoxicity of 6,7-dihydroxy-substituted coumarins (65). Hydroxycoumarins with a nitro group in the aromatic ring also showed a selective dose- and time-dependent antiproliferative effect in renal carcinoma cells, normal human skin fibroblast cells (HS613.SK) and malignant melanocytes (SK-MEL-31) (66,67,68) by modulating mitogen-activated protein kinases. Finn et al. (66) demonstrated the selective and irreversible cytotoxicity of 6-nitro-7-hydroxycoumarin on human renal carcinoma cells, in contrast to the reversible cytotoxicity of 7,8-dihydroxycoumarin. Mobility shift and BrdU incorporation assays showed that both compounds do not intercalate the DNA molecule, but have a concentration-dependent inhibitory effect on its synthesis, pointing to a possible therapeutic role in renal cell carcinoma.

Warfarin and coumarin have been shown to inhibit tumor spread and stimulate granulocytes, lymphocytes and macrophages, which warrants their use as maintenance therapy in the treatment of melanoma (69). Velasco-Velazquez et al. (70) demonstrated this effect in vitro for 4-NS using B16-F10 mammalian melanoma cell lines, while Thornes' (69) reports on the immunomodulatory activity of coumarin in malignant melanomas prompted research into its potential use in renal carcinoma. and prostate cancer and this antitumor effect was further validated by other investigators on a range of cell lines (786-O, A-498, DU145, LNCaP) and in human subjects (71).

The anticoagulant effect of coumarins may also prevent tumor spread by reducing malignant cell adhesion and tumor angiogenesis, limiting the ability of tumor cells to retain within the microvasculature. This effect

is confirmed by results related to the treatment of small cell lung cancer and other types of cancer with warfarin (72).

Simple coumarins can be used not only for the treatment of cancer, but also for the side effects caused by radiotherapy, because of the beneficial effects in radiogenic sialoadenitis and mucositis (73). This is confirmed by a study in which the efficacy of coumarin/troxerutin combination therapy to protect salivary glands and mucosa in patients undergoing head and neck radiotherapy was investigated (73). Coumarin and a number of other benzpyrones also successfully reduce protein edema (eg lymphoedema) present in many cancer conditions (74). However, Loprinzi et al. (75) reported that coumarin treatment was not an effective therapy in women with arm lymphedema after breast cancer treatment, emphasizing that the beneficial anti-inflammatory effect could be increased by combining coumarin with other compounds or by finding new more effective coumarin derivatives.

6. Conclusions

From this summary we can conclude that the heterocyclic rings of coumarin are important pharmacophores in contemporary pharmacotherapy that motivates many scientific researchers to synthesize new compounds rich in coumarin rings together with the development of new methods for their synthesis. It is also worth mentioning that recently many studies of coumarin derivatives are oriented to evaluate the anticancer effect and their application in various targets of anticancer therapy.

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