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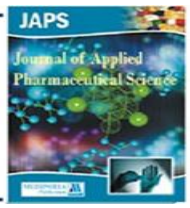

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Coumarin: Chemical and Pharmacological Profile

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ABSTRACT

Coumarins are classified as a member of the benzopyrone family. all of which consist of a benzene ring joined to a pyrone ring. The benzopyrones can be subdivided into the benzo-alfa-pyrones to which the coumarins belong and the benzo-gama-pyrones, of which the flavonoids are principal members. Umbelliferone, esculetin and scopoletin are the most widespread coumarins in nature. During the synthesis of these compounds ortho-hydroxylation should respectively take place on p-coumaric, caffeic and ferulic acid. The coumarins are of great interest due to their pharmacological properties. In particular, their physiological, bacteriostatic and anti-tumor activity makes these compounds attractive backbone derivatisation and screening as novel therapeutic agents.

Keywords: coumarin, benzopyrone, flavonoids, anti-tumor activity, bacteriostatic

INTRODUCTION

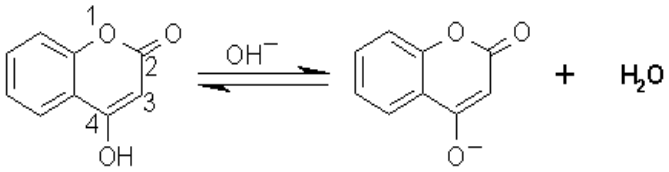
Coumarins owe their class name to ‘Coumarou’, the vernacular name of the tonka bean (*Dipteryx odorata* Willd, Fabaceae), from which coumarin, it was isolated in 1820 (Bruneton, 1999). There are four main coumarin sub-types: the simple coumarins, furanocoumarins, pyranocoumarins and the pyrone-substituted coumarins. The simple coumarins (e.g. coumarin,7-hydroxycoumarin and 6,7-dihydroxycoumarin), are the hydroxylated, alkoxylated and alkylated derivatives of the parent compound, coumarin, along with their glycosides. Furanocoumarins consist of a five-membered furan ring attached to the coumarin nucleus, divided into linear or angular types with substitution at one or both of the remaining benzoid positions (Ojala T., 2001). Pyranocoumarin members are analogous to the furanocoumarins, but contain a six-membered ring. Coumarins substituted in the pyrone ring include 4-hydroxycoumarin (Keating *et al*, 1997).The synthetic compound, warfarin, belongs to this coumarin subtype. By virtue of its structural simplicity coumarin has been assigned as head of the benzo-alpha-pyrone, although it is generally accepted that 7-hydroxycoumarin be regarded as the parent compound of the more complex coumarins (Murray *et al*, 1982). Genistein is an isoflavone and belongs to the benzo-gama-pyrones. It is a natural component of soy and has been intensively investigated as a chemopreventitive agent, mainly against hormonally regulated breast and prostate cancers in animal models (Constantinou *et al*, 1990, Finn *et al*, 2002).

Coumarins comprise a very large class of compounds found throughout the plant kingdom. They are found at high levels in some essential oils, particularly cinnamon bark oil (7,000 ppm), cassia leaf oil (up to 87,300 ppm) and lavender oil. Coumarin is also found in fruits (e.g. bilberry, cloudberry), green tea and other foods such as chicory (Lake, 1999). Most coumarins occur in higher plants, with the richest sources being the Rutaceae and Umbelliferone. Although distributed throughout all parts of the plant, the coumarins occur at the highest levels in the fruits, followed by the roots, stems and leaves. Environmental conditions and seasonal changes can influence the occurrence in diverse parts of the plant. Recently six new minor coumarins have been isolated from the fruits and the stem bark of *Calophyllum dispar* (Clusiaceae). The genus *Calophyllum*, which comprises 200 species, is widely distributed in the tropical rain forest where several species are used in folk medicine (Guilet *et al*, 2001). Although most of the natural coumarins in existence have been isolated from the higher plants, some members have been discovered in microorganisms. Some important coumarin members have been isolated from microbial sources e.g. novobiocin and coumermycin from *Streptomyces*, and aflatoxins from *Aspergillus* species (Cooke *et al*, 1997, Cooke, 1999).

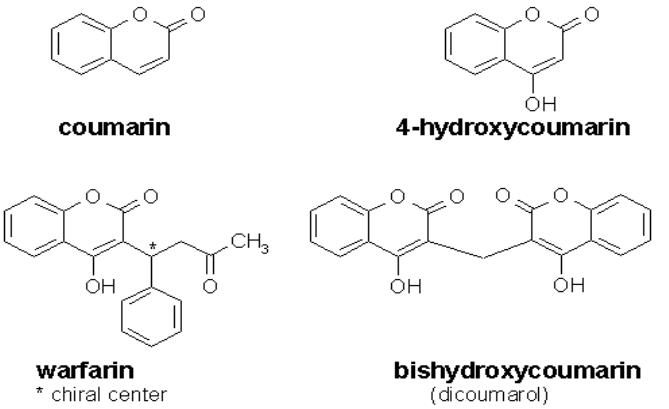
Chemical Profile

Structure

Coumarin and its derivatives are principal oral anticoagulants. Coumarin is water insoluble; however 4-hydroxy substitution confers weakly acidic properties to the molecule that makes it water soluble under slightly alkaline conditions.

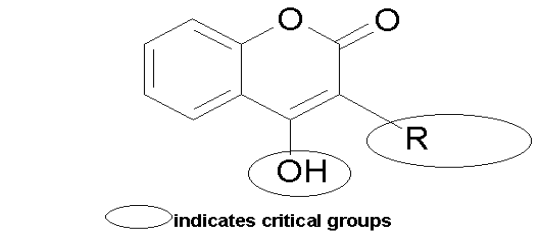


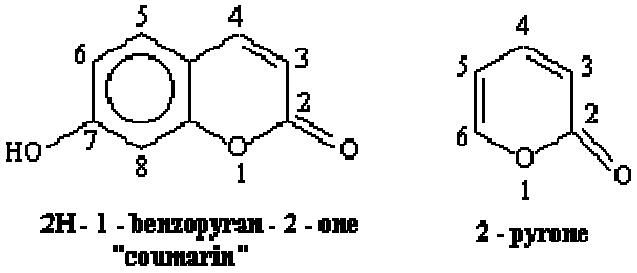
The structures of coumarin and its derivatives are as shown below. Warfarin is marketed as the sodium salt. It has one chiral center. The S (-) isomer is about 5 - 8 times more potent than the R (+) isomer; however, commercial warfarin is a racemic mixture.



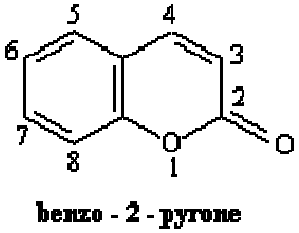
Structure Activity Relationships

Coumarin and 4-hydroxycoumarin do not possess anticoagulant activity. Link, who pioneered the isolation and characterization of bis' hydroxycoumarin (dicoumarol) from sweet clover, concluded that the minimal requirements for anticoagulant activity are 4-hydroxy group, a 3-substituent, and a bis molecule (Chen *et al*, 2001).

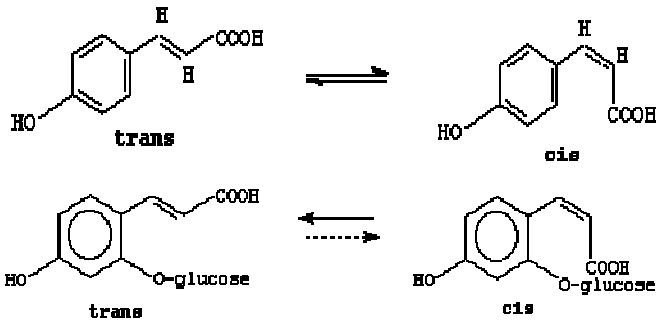




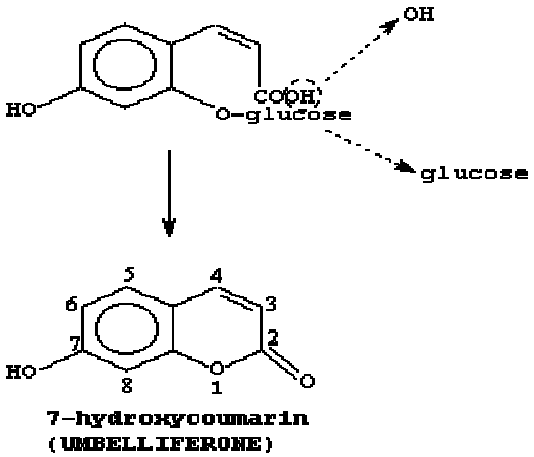
The benzo-2-pyrone nucleus of the simple coumarins derives from the phenyl acrylic skeleton of cinnamic acids.



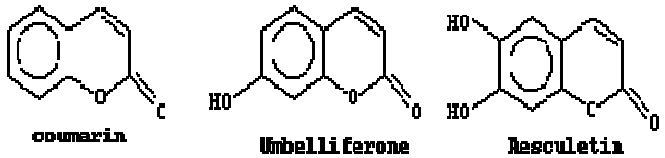
The coumarin structure is derived from cinnamic acid via ortho-hydroxylation, trans-cis isomerisation of the side chain double bond and lactonisation. The Trans form is stable and could not cyclise, therefore, there should be isomerisation of some sort and the enzyme isomerase is implicated.

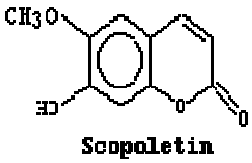


The cis form is very unstable, therefore, will tend to go to the Trans configuration. Glucose is a leaving group which assists in the cis-trans transformation. A specific enzyme found in *Melilotus Alba (Leguminosae)* specifically hydrolyses the cis-glucoside (beta-glucosidase).



Umbelliferone, esculetin and scopoletin are the most widespread coumarins in nature. Thus this biosynthesis pathway showed that all coumarins oxygenated at position 7(Desai, 2005, Friedli, 2001).





Pharmacological Profile

Due to its biochemical properties coumarin were proposed for use in clinical medicine. they should be evaluated for the treatment of various clinical conditions.

High Protein edema (HPE)

The lymph system is responsible for drainage of interstitial fluid within human tissues. edema interferes with the metabolism of the tissue cells and reduces oxygen transport, resulting in problematic wound healing. In the case of high protein edemas (HPO), there is an accumulation of protein in the tissue following trauma or inflammation, with resulting permeability of the capillaries causing water leakage in the tissue species (Velasco-Velazquez *et al*, 2003). Many disease states are associated with high protein edemas, ranging from extremely severe and chronic (*e.g.* lymph edema and elephantiasis) through more common and acute forms (*e.g.* burns, accidental and surgical traumas). Coumarin and numerous other benzopyrones have been tested in high protein edema, and able to subsidize swelling. However, according to Loprinzi and colleagues, coumarin treatment alone is not effective therapy for women who have lymph edema of the arm after treatment for breast cancer. It may be possible to increase the beneficial therapeutic effect of coumarin by using it with other compounds into main combination treatments (Ebbinghaus *et al*, 1997). The objective of a recent study was to evaluate the edema-protective effect of a combination vasoactive drug, coumarin/troxerutin (SB-LOT) plus compression stockings in patients suffering from chronic venous insufficiency after decongestion of the legs as recommended by the new guidelines. The study confirms the edema-protective effect of SB-LOT in chronic venous insufficiency and provides a treatment option for patients who discontinue compression after a short time (Vuky *et al*, 2000).

- **Chronic Infections**

In addition to its stimulatory effect on macrophages, coumarin has been shown to activate other cells of the immune system. In chronic brucellosis *Brucella abortis* infects macrophages, thus eluding the immune response (Thornes *et al*, 1982).When immunostimulatory drugs such as coumarin are administered, and the symptoms of chronic brucellosis disappear. These results have encouraged the use of coumarin in other chronic infections such as mononucleosis, mycoplasmosis, toxoplasmosis and Q fever. A new antiplasmodial coumarin has been isolated from the roots of *Toddalia asiatica.* This finding supports the traditional use of this plant for the treatment of malaria (Dexeus *et al*, 1990).

Cancer treatment

Anti-cancer drugs have traditionally been targeted to damage the aberrantly dividing cell by interrupting the cell division process. Reagents used include DNA intercalating agents (*e.g.* Adriamycin), DNA cross-linking agents (*e.g.*cis-platin), topoisomerase inhibitors (*e.g.* campothecins), cytoskeleton-disrupting agents (*e.g.* vinblastin) and antimetabolites (*e.g.* mercaptopurine). These drugs are effective, and cytotoxic, and thus exhibit severe side effects, particularly on normal proliferating tissues such as the haematopoietic system (Kokron *et al*, 1991, Marshall *et al*, 1991, Bosland, 1991).Often combination therapies, whereby several cytotoxic agents are combined in the treatment regime, offer better results with fewer toxic side-effects, as they are carefully regulated to allow recovery of normal, but not malignant cells, from drug exposure. Currently, chemotherapy, radiotherapy and surgery combined offer the best outcomes for cancer patients and treatment combinations have been successfully applied to particular cancer types, for example, Hodgkin's lymphoma, testicular cancer and various leukemia. Coumarins can be used not only to treat cancer but to treat the side effects caused by radiotherapy (Agarwal, 2000, Marshall *et al*, 1990).A recent study

investigated the efficacy of coumarin/troxerutin combination therapy for the protection of salivary glands and mucosa in patients undergoing head and neck radiotherapy. The results suggest that coumarin/troxerutin have a favorable effect in the treatment of radiogenic sialadentis and mucositis (Mahler *et al*, 1992). The interest in coumarin and 7-hydroxycoumarin as anti-cancer agents arose from reports that these agents had achieved objective responses in some patients with advanced malignancies (Myers *et al*, 1994).

Blood Coagulation and Anticoagulant

The physiological systems that control blood fluidity are both complex and elegant. Blood must remain fluid within the vasculature and yet clot quickly when exposed to no endothelial surfaces at sites of vascular injury. When intravascular thrombi do occur, a system of fibrinolysis is activated to restore fluidity. A delicate balance prevents both thrombosis and hemorrhages and allows physiological fibrinolysis without excess pathological fibrinogenolysis. The drugs described in this article have very different mechanisms of action, but all alter the balance between procoagulant and anticoagulant reactions. With these drugs, efficacy and toxicity are necessarily intertwined. For example, the desired therapeutic effect of anticoagulation can be offset by the toxic effect of bleeding due to overdosing of anticoagulant. Similarly, overstimulation of fibrinolysis can lead to systemic destruction of Fibrinogen and coagulation factors. The predominant agents for controlling blood fluidity, including-parenteral anticoagulant heparin and its derivatives, which stimulate a natural inhibitor of coagulant proteases. The coumarin as anticoagulants, which block multiple steps in the coagulation cascade. Fibrinolysis agents, which lyse pathological thrombi. Anti platelet agents, especially aspirin. The pathway of clot removal, fibrinolysis, along with sites of action of fibrinolysis agents. Coumarins are competitive inhibitors of vitamin-K in the biosynthesis of prothrombin. The coagulation cascade relies on the conversion of prothrombin to thrombin in a very important step under the condition (Goodman & Gilman's, 2006).

Inflammation

The inflammatory process is the response to an injurious stimulus. It can be evoked by a wide variety of noxious agents (*e.g.*, infections, antibodies, or physical injuries). The ability to mount an inflammatory response is essential for survival in the face of environmental pathogens and injury; in some situations and diseases, the inflammatory response may be exaggerated and sustained without apparent benefit and even with severe adverse consequences. No matter what the initiating stimulus, the classic inflammatory response include warm, pain, redness, swelling. It has been proposed that some, but not all, NSAIDs may interfere with adhesion by inhibiting expression or activity of certain of these cell-adhesion molecules. Novel classes of anti-inflammatory drugs directed against cell-adhesion molecules are under active development but have not yet entered the clinical area. Coumarin and their derivatives are highly effective against inflammatory response (Goodman & Gilman's, 2006).

CONCLUSION

The coumarins are of great interest due to their biological properties. Their physiological, bacteriostatic and anti-tumor activity makes these compounds attractive for further backbone derivatisation and screening as novel therapeutic agents. Weber and co-workers have shown that coumarin and its metabolite 7-hydroxycoumarin have antitumor activity against several human tumor cell lines. Both coumarin and coumarin derivatives have shown promise as potential inhibitors of cellular proliferation in various carcinoma cell lines. In addition it has been shown that 4-hydroxycoumarin and 7-hydroxycoumarin inhibited cell proliferation in a gastric carcinoma cell.

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