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Therapeutic Role of Coumarins and Coumarin-Related Compounds

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Abstract

"Colorless, crystalline and natural", a simple description for a group of compounds with multiple therapeutic effects, found throughout the plant kingdom. Coumarins have a significant effect on physiological, bacteriostatic and anti-tumor activity. Our article is a brief overview of the therapeutic functions of coumarins and coumarin related compounds.

Keywords: Coumarin; Anti-tumor activity; Anticoagulant

Introduction

Coumarins are a group of polyphenolic compounds isolated from plant product Tonka bean, *coumarou* in 1820. Coumarins are colorless and crystalline phytochemical substances [1]. It is an oxygen heterocycle, which occurs either in free or combined form with glucose. They belong to the family of benzopyrones, which consists of benzene ring joined by a pyrone ring Figure 1 [2,3]. Benzopyrones are subdivided into benzo-α-pyrones and benzo-γ-pyrones of which coumarins and flavonoids are prime members of benzo-α-pyrones and benzo- γ –pyrones class respectively. The biochemical, pharmacological and therapeutic applications of simple coumarins could be influenced by the substitution pattern. Studies have proven that coumarins act as competitive inhibitors of vitamin K. Other intricate compounds are based on the coumarin nucleus which comprises of the anticoagulants like warfarin, aflatoxins and the psoralens [4]. Studies have also shown that they function as blood diluting agent and also exhibits anti-fungicidal property. Researches have also proved the selective cytotoxicity of coumarins for tumor cells and also the effect of coumarins in the regulation of immune response, cell growth and differentiation [5]. Nowadays, coumarins are also used as additives in food and cosmetic industry, as laser dyes, agrochemical industries and also as optical brightening agents. Studies have proven that it possesses anti-aging, and cardioprotective function.

Occurrence

The four main classifications of coumarins are simple coumarins, furanocoumarins, pyrano coumarins and pyrone substituted coumarins [6]. The features of four main coumarin subtypes are listed in the Table 1 and Figure 1. Coumarin covers a very wide range of compounds throughout the plant kingdom and are found rich in fruits, roots, stems and leaves. They are rich in cassia leaf oil, lavender oil and cinnamon bark oil. Richest sources are found in Rutaceae and Umbelliferone. Coumarins are also found in selective microorganisms. Members of coumarins isolated from microbial sources are novobiocin from *Streptomycin* and aflatoxin from *Aspergillus species*. They are also used as enhancing agent in cosmetic products like perfumes, soap, detergents, toothpaste and alcoholic beverages [7]. It is also used as a neutralizer in rubber and plastic materials and also in paints and sprays to dilute the unpleasant odors [8].

Therapeutic Functions of Coumarins and Coumarin Derivatives

Coumarins possess a wide range of pharmaceutical actions and biological functions and has great importance in the use of medicine and also used for treating various clinical conditions. They exhibit significant pharmacokinetic activity due to its rapid absorption and metabolism [9] in the body. Coumarins have a significant effect on physiological, bacteriostatic and anti-tumor activity. Table 2 shows the list of coumarins and its therapeutic functions.

Anticoagulant function

Coumarin derivatives are also prime oral anticoagulants. They exhibit therapeutic effect by acting as competitive inhibitors in the coagulation cascade pathway. They inhibit the function of vitamin K which is required for the biosynthesis of prothrombin. Thus, coumarins exhibit a desired therapeutic effect of anticoagulation by controlling blood fluidity and removal of toxic effect of bleeding [10].

Treatment of Cancer

The mechanism of action of anti-tumor drugs is basically to target the dividing cells that disturb cell division. Although new techniques like chemotherapy and radiotherapy provide best results for the treatment for cancer it triggers various side effects. Coumarins are effective not only for treatment of cancer, but also to treat the side effects caused by radiotherapy. Coumarins are very significant in the treatment of cancer and is used in the treatment of prostate cancer, renal cell carcinoma and leukemia [11,12]. Coumarins have found to have good maintenance therapy in case of melanoma and also found to inhibit the spread of tumors. Coumarins are very significant in the treatment of cancer due to its non- toxic, anticoagulant property. Coumarins have a cytotoxic mechanism and used as cell lines and has a potential therapeutic function in renal cell carcinoma [13]. Coumarin due to its hormonal sensitivity and immune modulating effects is significant in the treatment of prostate cancer. Coumarin derivatives like furanocomarins, pyranocoumarins, isoflavones, benzopyrones have a significant role in the treatment of different cancer conditions.

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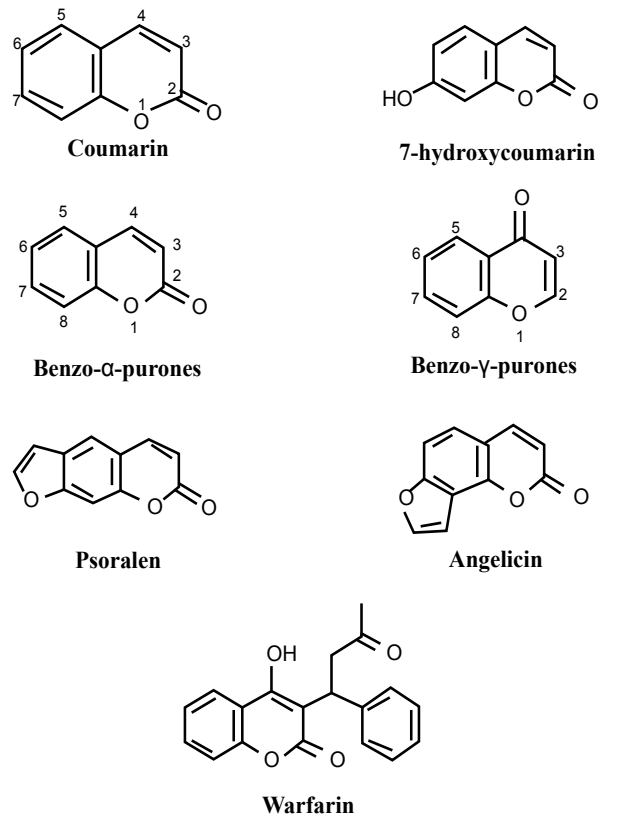

Figure 1: Structure of Coumarins.

Coumarin Subtypes	Structural features	Examples
Simple Coumarins	Hydrolylated, alkoxylated or alkylated benzene ring	Coumarin 4-hydroxycoumarin
Furanocoumarins	Furan ring attached to benzene ring	Psoralen Angelicin
Pyranocoumarins	Pyran ring attached to benzene ring	Seselin Xanthylein
Pyrone-Substituted Coumarins	Substitution on pyrone ring	Warfarin

Table 1: Classification of Coumarin, its structural features and examples.

Coumarin	Therapeutic Role
Warfarin 4-hydroxycoumarin	Malignant melanoma
Pyranocoumarins	Renal cell carcinoma
Pyranocoumarins	Prostate cancer
Coumarin 7-hydroxycoumarin	Leukemia
Benzopyrones	Breast Cancer
Psoralens	Cervical Carcinoma
Psoralens	Skin disorders like Mycosis fungoides, Psoriasis, Vitiligo
Warfarin	Anticoagulant

Table 2: Coumarins and its therapeutic role.

Chronic infections

Coumarins are used as immunostimulatory drug for the treatment of chronic infections. The mechanism of action involves the activation of macrophages inducing the cells of the immune response. Coumarins are used in the treatment of chronic infections like mononucleosis, toxoplasmosis, Q-fever, mycoplasmosis and chronic brucellosis [14]. Antiplasmodium drug isolated from the roots of *Toddalia asiatica* is used in the treatment of malaria.

Inflammation

Inflammatory mechanism is due to an injury or effect of infectious agents. Coumarins are potent anti-inflammatory drugs and it directs against cell-adhesion molecules, thus highly significant in inflammatory responses [10].

Edema

Coumarins have potent edema protective function and thus involved in the treatment of lymphedema, elephantiasis and other high protein edema conditions [15]. Edema results in the accumulation of protein, resulting in delayed wound healing. Benzopyrones are effective for the treatment of high protein edema. Several studies have shown that coumarin reduces edema in rodents caused due to thermal damage by effectively reducing the level of protein in the tissues [15,16]. Administration of coumarins along with vasoactive drugs has a very high beneficial effect in the treatment of edema. Studies have reported that the action of coumarin is by the binding to the plasma proteins and thereafter activate the macrophage and proteolysis [17].

Conclusion

The coumarins are of great attention due to their therapeutic property. Their physiological, bacteriostatic and anti-tumor activity marks coumarins as novel ones for therapeutic applications. Several researchers have reported the clinical applications of coumarins and coumarin derivatives in the treatment of several diseases. Several studies have proven multiple potential role of coumarins which includes disease spread and prevention, growth modulation, anti-oxidant and anti-tumor effects.

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