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REVIEW ARTICLE

Biological Evidences of Dicoumarol: A Review

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ABSTRACT

Dicoumarol, a natural anticoagulant drug chemically designated as is metabolized from Coumarin in the sweet clover (*Melilotus alba* and *Melilotus officinalis*) by molds, such as *Penicillium nigricans* and *Penicillium jensi*. Coumarin (1,2-benzopyrone), the parent molecule of Dicoumarol, is the simplest compound of a large class of naturally occurring phenolic substances made of fused Benzene and Pyrone rings . In addition, the Coumarin anticoagulants, Dicoumarol (Dicumarol) and its synthetic derivative Warfarin sodium (Coumadin), have been shown to decrease metastases in experimental animals. Warfarin sodium, largely replacing Dicoumarol therapeutically as an anticoagulant, has been used for the treatment of a variety of cancers and shown to improve tumor response rates and survival in patients with several types of cancer. However, despite numerous studies, little information has been acquired on the cellular mechanism of action of Coumarin compounds in the treatment of malignancies. Possibly for this reason, the Coumarin compounds have not received much attention for the treatment of cancer.

Keywords: Dicoumarol, Chemical compounds, Plants, Bioactivities

INTRODUCTION

Phytochemicals are chemical compounds that occur naturally in the plant kingdom. Some are responsible for the organoleptic properties of the natural sources in which they are present. The term is generally used to refer to those chemicals that may have biological significance, for example carotenoids, flavonoids, coumarins, or chromones, but not all are established as essential nutrients. There may be as many as 4,000 different phytochemicals having potential activity against several diseases such as cancer and metabolic or degenerative diseases. Coumarins have been isolated from hundreds of plants species distributed in more than 40 different families. There were isolated more than different 1300 coumarins, well distributed in Angiospermae, Monocotyledoneae and Dicotyledoneae families. Coumarinic compounds are a class of lactones structurally constructed by a benzene ring fused to α-pyrone ring, and essentially possess-conjugated system with rich electron and good charge-transport properties (Murray *et.al*., 1982 & Murray RDH 1997).

Dicoumarol, a symmetrical biscoumarin can be considered as the "parent" of the widely used anticoagulant drug, warfarin. The discovery of dicoumarol's bioactive properties resulted from an investigation into a mysterious cattle disease in the 1940s. Dicoumarol (3,3'-methylenebis(4-hydroxy-2H-chromen-2-one). It was subsequently identified as a fungal metabolite of coumarin and the main cause of sweet clover disease, a haemorrhagic disease of cows and other livestock (Campbell & Link, 1941; Gomez-Outes *et. al*. 2012). Dicoumarol can fatally inhibit clotting in farm animals, it was used pharmacologically as an anticoagulant (Greisman & Marcus, 1948). It also had some use as a rat poison in agriculture (Armour & Barnett, 1950). However, in both applications it was superseded by the related compound warfarin (Keeling et al, 2011; Tadros & Shakib, 2010).

Warfarin has the advantage of being more potent than dicoumarol and the sodium salt can be administered orally or by injection (Link, 1959) Dicoumarol continued to be used in the laboratory for a variety of applications, including as an uncoupler of the mitochondrial or bacterial membrane proton motive force (Van & Slater ,2015-2019). In recent years, it has once again been receiving attention as a potential lead molecule in drug discovery–this time for anti-cancer agents, rather than for anticoagulants. This review gave the major bioactivities of dicoumarol compound.

BIOLOGICAL ACTIVITIES

Anticoagulant effect

Coagulation refers to the physiological process that blood flows from a flowing liquid state to a non-flowing gel state. The essence of coagulation is the process that soluble fibrinogen in plasma changes into insoluble fibrin. Vitamin K is necessary for the liver synthesis of coagulation factors and thus antagonists of vitamin K can be used as anticoagulants in clinical practice (Norm et al, 2014). Dicoumarol has a similar core structure with vitamin K. Hence it can competitively antagonize with vitamin K and inhibit the synthesis Of coagulation factors in the liver. Further studies showed that vitamin K epoxide reductase complex subunit 1 (VKORC1), a vitamin K cyclase, is the target of dicoumarol (Wallin et al, 2008).

Anticancer effect

Dicoumarol exerts an inhibitory effect on cell viability, cell proliferation, and induces apoptosis in a variety of cancers such as cholangiocarcinoma, osteosarcoma, mastadenoma, leucocythemia, renal carcinoma, and melanoma. Dicoumarol ligand with sodium adduct exerts cytotoxicity in U2OS human bone osteosarcoma epithelial cells (Rehman et al, 2013). Dicoumarol arrests the cell cycle in G0/1 phase by increasing the cellular superoxide in HL-60 human myeloid leukemia cells (Bello et al, 2005). It induces apoptosis of cancer cells in a concentration- and time-dependent manner, which was mediated by oxidative stress, cytochrome c release followed by activation of caspase-9 and cleavage of caspase-3 (Cullen et al 2003). Furthermore, it induces apoptosis in MCF-7 breast cancer cells but shows no toxicity on oocyte maturation and ovarian tissues of the mouse (Aras et al, 2015).

Antimicrobial and antiviral activities

Dicoumarol and a series of its derivatives containing Cu2+ complexes exerted the antibacterial activity including gram-positive bacterium *Bacillus subtilis* ATCC11774 and *Streptococcus pyogenes* ATCC12384), m-negative bacterium (*Pseudomonas aeruginosa* ATCC25619 and herichia coli ATCC25922) and Mycobacterium tuberculosis H37Ra. It also exerts antifungal activity like *Aspergillus niger* ATCC64958 and *Candida albicans* ATCC66027 (Dholaria et al, 2013; Tian et al, 2013). 2-Pyridinodicoumarol (2-PyDC), dicoumarol derivative, exerts antibacterial activity in four *Staphylocus aureus* bacterial strains, including *S. aureus* ATCC 29213, MRSA 75302, Mu50 and USA 300 LAC with the minimal inhibitory concentration (MIC) ranging from 16 to 64 µg/mL (Hou et al, 2014). Dicoumarol inhibits coli nitroreductase enzyme, an activating enzyme for nitroaromatic drugs of the dinitrobenzamide class (Johanson et al, 2003).

Neurotoxicity

The neurotoxicity of dicoumarol may result from its inhibition of NQO1, which plays a protective role in the dopaminergic system of the substantia nigra striatum (Diaz-Veliz et al, 2004). Thus, as an inhibitor of NQO1, dicoumarol may increase the damage to the nigrostriatal dopaminergic system when used in combination with other medicines. For instance, a combination of aminochrome and dicoumarol for 48h induced. Approximately 70 % cell death in the RCSN-3 neuronal dopaminergic cell line (Munoz et al, 2012).

Hepatotoxicity and lymphotoxicity

Liver-specific side effects are rare in dicoumarol treatment, but there are reports of inflammatory infiltration, hepatocyte necrosis, and liver failure. Therefore, transaminase and cholestasis parameters should be checked regularly. If there is unclear liver disease, the medication treatment should be weaned off immediately (Castedal, 1998). Dicoumarol enhanced the production of menadione induced strand breaks in isolated human lymphocytes (Woods et al, 1997). In the absence of serum, dicoumarol showed significant cytotoxicity to HL-60 cells (Forthoffer et al, 2002).

CONCLUSION

This review showed the importance of dicoumarol as a medicinal compound. The discovery of dicoumarol as an anticoagulant is an example, which opens the development of coumarins anticoagulant drugs as warfarin, acenocoumarol, ethyl biscoumacetate, etc. The main mechanism of this category of drug is by interfering with the metabolism of vitamin K. Beside its anticoagulant effect, dicoumarol and its derivatives show anticancer, antimicrobial, antiviral activities. Furthermore, other targets for dicoumarol such as NQO1 have been identified, which might provide potential applications other than an anticoagulant. However, the side reactions, especially hemorrhagic complications, need to be avoided in clinical practice though it has been used for several decades.

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