Chapter

From Rat Poison to Medicine: Medical Applications of Coumarin Derivatives

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Abstract

Historical reports mention the application of medicinal plants containing coumarins against various ailments. Current research suggests that at least some of the actions described may be attributable to the action of these coumarins. Warfarin and its derivatives are coumarins used today in medical practice. Their mechanism of action lies in the competitive antagonism of vitamin K, through which they inhibit coagulation in the body by preventing the production of prothrombin. Due to this action, these coumarins are a major group of drugs with anticoagulant activity. Anticoagulants reduce the risks of undesirable blood clots leading to myocardial infarction, pulmonary embolism, and ischemic stroke among others. The anticoagulant activity can also lead to undesired bleeding. Extreme caution is warranted when given to menstruating women, patients suffering from disorders prone to bleeding like gastric ulcer and rheumatoid arthritis, and to persons with a high likelihood of blunt and sharp trauma. In addition, there is a significant augmentation of the anticoagulant activity when used in combination with non-steroidal anti-inflammatory agents and agents interfering with the metabolism of the coumarins. Recent findings propose additional uses like anti-tumor and antibiotic actions for coumarins. The clinical application of these actions has yet to be demonstrated.

Keywords: warfarin, coumarin, anticoagulant, prothrombin, coagulation cascade, adverse reaction, rodenticide, embryopathy, vitamin K

1. Introduction

Coumarins are members of the benzopyrone class of organic compounds that are found in many plants [1] and possess a variety of pharmacological properties such as antimicrobial, anti-inflammatory, antidiabetic, and antioxidant activity, as well as a significant influence on physiological processes like enzyme inhibitory activity [2]. Despite the wide availability of coumarins and their lead compounds and metabolites in natural products [3], their application up till now has been mostly limited to the anticoagulant activity of warfarin derived from dicoumarol and its analogues [4]. The mechanism of action of these anticoagulants lies in the competitive antagonism of vitamin K, through which they inhibit coagulation of blood in the body by preventing the production of prothrombin and several other coagulation factors [5]. Due to this action, these coumarins are a major group of oral drugs with anticoagulant activity. Anticoagulants reduce the risks of undesirable

blood clots leading to myocardial infarction, pulmonary embolism, and ischemic stroke among others. This chapter gives an overview of medical applications of coumarins, in particular the history and evolution of warfarin and related compounds as important anticoagulant agents.

2. History

The medical application of plants containing coumarins probably started long before the isolation of this chemical compound from the Tonka bean in 1820 by Nicholas Jean Baptiste Gaston Guibourt [6]. Ancient Romans produced a cough syrup from the marshmallow (*Althea officinalis*) [7], which contains the coumarin scopoletin [8]. This coumarin demonstrated inhibition of leucocyte migration in mice [9], a process that can be linked to the alleged antitussive effect. Cough is a result of the reaction of the airways to leukotrienes and other factors secreted by leucocytes [10–12]. Inhibition of the migration of these to the affected region consequently reduces the availability of these paracrine factors. In addition, at least one of the herbs mentioned by the famous Roman General Pliny in his pharmacopeia [13] contain coumarins with proven action. For example, the extracts of the common rue or herb-of-grace *Ruta graveolens* contain xanthotoxin [14], a coumarin that reduces the mobility of human spermatozoa possibly through inhibition of membranaeous potassium channels [15].

The application of coumarin and its derivatives in current western medicine dates to the fifties of the past century with the clinical recognition of coumarins as anticoagulant agents. This event was the result of observations of poisoning of animals with coumarin derivatives that led to massive internal organ bleeding [16]. Soon it became clear that the substance that was responsible for the deadly internal bleeding of cattle was dicoumarol [17]. Shortly after this, the proposal was made to develop a coumarin derivative with rodent killing ability and gradually warfarin found its application as a potent rodenticide [18]. When it became clear that this substance also led to bleeding disorders after poisoning in human beings [19], its application as a therapeutic anticoagulant found its way in medicine [20, 21]. Seven decades later, warfarin is still in use as an anticoagulant [22]. In the meantime, several other coumarins with anticoagulant properties like acenocoumarol, phenprocoumon, and fluindione have been developed, and they are used in a variety of clinical settings [23–25].

3. Physiology of hemostasis

Hemostasis in mammals and humans is the result of three sequential processes. The first of these is the acute vasoconstriction within seconds after damaged arteries and veins, by local activity of the potent vasoconstrictor thromboxane among others [26]. The second step is the formation of a blood clot through the entrapment of platelets by fibrin within hours and finally followed by the organization of the fibrin mesh into an adhesive structure on the vessel wall [27]. In one of the last steps of the coagulation, prothrombin converts to thrombin, an enzyme that converts the plasma protein fibrinogen to fibrin monomers and activates factor XIII of the coagulation cascade. Activated factor XIII synthesizes fibrin from these monomers. The acquired fibrin molecules then trap the platelets and eventually form the blood clot [27, 28]. The coagulation process has both an intrinsic and an extrinsic pathway. The difference is that the intrinsic pathway only requires ionized calcium to be activated while the extrinsic pathway requires both calcium and tissue factor that

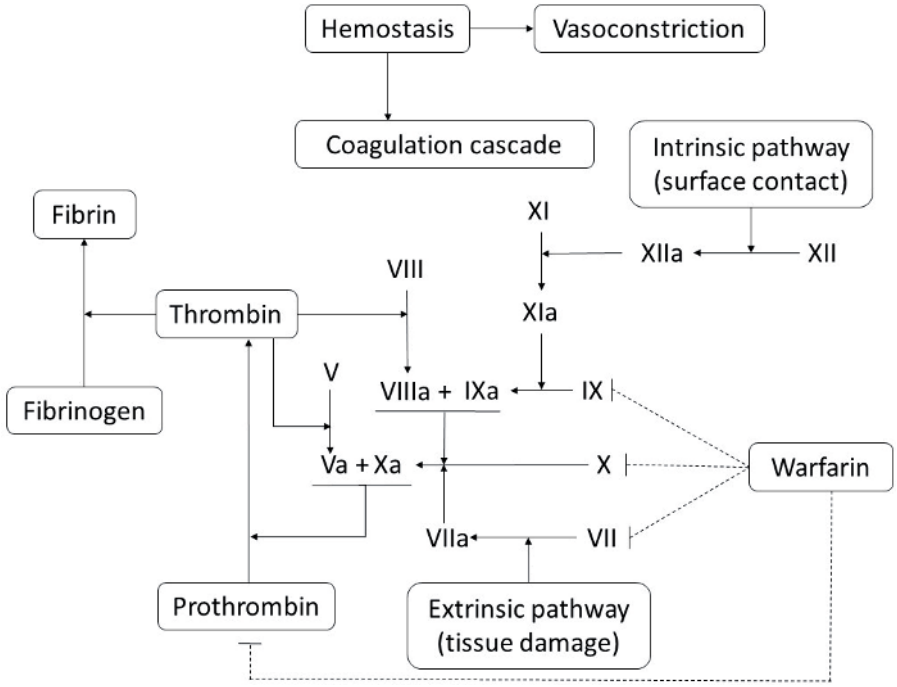

Figure 1.
Overview of the coagulation process along with the interference sites of warfarin.

is released with trauma [28]. **Figure 1** gives an overview of the coagulation process along with the interference sites of warfarin.

4. Pharmacology

4.1 Pharmacokinetics

Warfarin is highly lipid soluble [29–31]. Between 70 and 100% of the oral intake is rapidly absorbed by the intestines with a maximum plasma concentration within 2 h after oral intake [30]. The half-life of the drug is generally more than 20 h, with a large individual variety [32]. Due to the overt lipid solubility, the major part of the drug is protein bound with less than 3% being biologically available [29]. Consequently, the agent has a slow onset of action and a long duration of activity [33]. In fact, the optimal effect is delayed for a few days, until all remaining activated factors II, VII, IX, and X are depleted from the liver and the circulation [33]. Warfarin accumulates in the liver where it exerts its effect and is inactivated through oxidative metabolism by cytochromes P450 to several isomers of water-soluble hydroxywarfarin with negligible anticoagulant activity [34, 35]. These metabolites are almost completely cleared by the kidneys [36]. The hepatic accumulation and relative easy absorption in the intestines result in an enterohepatic circulation of the drug [37]. Enterohepatic circulation is a process in which substances are secreted by the liver with bile to the intestines and subsequently absorbed again by the latter [28]. This results in recycling of the product with very little elimination.

4.2 Mechanism of action

Warfarin inhibits the enzyme vitamin K epoxide reductase that recycles oxidized vitamin K [38]. Vitamin K activates the coagulating factors prothrombin

(factor II) and the structurally related serine proteases known as factors VII, IX, and X in the liver cells [27]. Decreasing the biological availability of vitamin K inhibits the synthesis of these essential factors and eventually leads to inhibition of the coagulation process. This means that this compound affects both the intrinsic as well as the extrinsic cascade of coagulation since prothrombin plays a central role in both of these pathways [28] and renders it a highly effective anticoagulant drug.

5. Indications and contraindications

Hemostasis is an essential process to prevent significant external as well as internal blood loss after injury. However, under certain circumstances, it is not desirable to activate or continue this homeostatic process like in disorders with spontaneous thrombosis such as deep venous thrombosis in the legs often resulting in pulmonary embolism [39]. In addition, there are conditions that are prone to a reasonable chance of forming a blood clot during stasis of the blood circulation like in atrial fibrillation and in the limbs of patients with prolonged immobility after surgery [39]. Moreover, conditions like myocardial infarction or ischemic stroke form a preventable group of disorders with inhibition of the thrombotic process [5]. Based on its anticoagulant properties, warfarin is thus an ideal compound for the treatment and prevention of these thromboembolic conditions [5].

Based on the pharmacokinetic properties and the challenges they present, dosing of warfarin is not simple, and a careful approach is necessary. On one hand, a low plasma concentration will not achieve the effect of sufficient anticoagulation and, on the other side of the spectrum, there is the constant chance of overdosing with potential lethal internal or external bleeding. Another problem is the great variety of absorption, body distribution, and metabolism of the agent with individual patients based on the pharmacokinetic properties of warfarin [30]. Frequent monitoring of therapeutic efficiency with adequate laboratory tools like prothrombin time (PT) or international normalized ratio (INR) is absolutely necessary [40, 41] and a fixed or constant dose is close to impossible. Nevertheless, warfarin is highly effective in anticoagulation regiments when carefully dosing and assessing the potential bleeding sites as well as other potential side effects. Warfarin is initially dosed at 5–10 mg daily [42]. Subsequent doses depend on the international normalized ratio, with a therapeutic value between 2 and 4. Concomitant administration of heparins like fraxiparine is necessary when fast anticoagulant activity is desirable [43].

Warfarin is not an ideal agent in conditions when immediate treatment of thromboembolism is imminent due to the long time of onset. In cases of pulmonary embolism and acute ischemic stroke, it is desirable to start with both the oral anticoagulant and fast-acting agent like heparins [44]. The long duration of action harbors another challenge. When acute termination of anticoagulation is necessary with unwanted bleeding like in menstruating women and after blunt and sharp trauma leading to hemorrhage, it could take days before the process of coagulation completely restores after quitting oral administration [27, 30] due to the depletion of coagulant factors in liver and blood. In these cases, intravenous administration of prothrombin complex, fresh frozen plasma with coagulation factors, and high doses of vitamin K may be helpful [45].

Warfarin readily passes the placenta and may result in spontaneous abortion due to retroplacental bleeding [46], as well as prematurity [47], fetal deformity [48], stillbirth [48], and fetal cranial bleeding [49]. Administration during the first trimester of pregnancy has a high risk of embryopathy [50]. This is accompanied by deformities of bone and cartilage [51], blindness, mental retardation, and other

neurologic abnormalities [52]. The occurrence of these complications and defects seem to be dose dependent [47, 53] and are most probably the result of the interference with vitamin K-dependent coagulation [38] and bone formation [54]. The effects of the central nervous system and the blindness are probably the result of microhemorrhages in the developing brain as a result of the anticoagulant activity [55]. Clotting factors are easily depleted in the fetus due to the immature liver and small circulating volume [46]. Warfarin does not enter breastmilk and is thus completely safe during lactation [56].

In conclusion, warfarin must be administered with great caution to women in their child-bearing age [57]. Therapy with this agent must be ceased immediately when it becomes clear that the patient is pregnant. Low-molecular weight heparins are a good alternative, since they do not cross the placenta and have been proven to be safe for mother, embryo, and fetus [58].

6. Drawbacks and side-effects

To say that anticoagulant coumarins have only a few side effects is an absolute understatement. Warfarin is one of the leading drugs with adverse effects requiring hospital admission [59]. Most of all, there is the constant chance of severe bleeding [60]. This can include internal hemorrhagic conditions in the head, gastrointestinal tract, female genitalia, the bladder and urethra or skeletal joints and muscles [40, 61]. They generally present as severe headache, stomach pain, and black or bloody stool, heavier than normal menstrual bleeding, discoloration of urine, and pain and swelling of the joints or muscles. Prolonged bleeding from external sharp or blunt wounds is always present [61]. All these conditions are the result of inability of the affected tissues to initiate and continue the process of hemostasis after damage to the epithelial barrier [62].

Patients suffering from hypertension, disorders of the liver, bleeding lesions, and the elderly and patients using drugs and substances that affect coagulation are at higher risk to suffer from bleeding when using warfarin [63]. Hypertension poses mechanical defects in the blood vessels, especially the arteries. Disorders of the liver reduce the ability of the body to eliminate the warfarin and thus make it more biologically available. In bleeding lesions, warfarin inhibits hemostasis. Among substances that can lead to bleeding when used with warfarin are steroidal and non-steroidal anti-inflammatory drugs, antibiotics, and alcohol. These potentiate the activity, interfere with the protein binding, and reduce the metabolism of warfarin, respectively [63]. Other side effects include injury to the kidneys with potential nephritis [64–66], inflammation of the skin [67] and blood vessels [66], and potentiation of rhabdomyolysis by simvastatin [64].

Due to resistance of rodents against warfarin, superwarfarins have been created [68]. These have a much longer time of activity and hence need only to be consumed once by the rodents, contrary to warfarin. The result however is that their effect persists much longer when deliberately or accidently consumed by humans [69] and treatment of this intoxication is a more challenging enterprise.

7. Interaction with drugs and foods

The efficacy of the anticoagulant treatment with warfarin highly depends on its bioavailability, since inhibition of the target (epoxy reductase) enzyme depends on direct binding of the drug to this protein [38]. In addition, vitamin K from external sources does not rely on recycling through this enzyme [38]. Hence, the absorption,

	Agent	Category	Possible mechanism	Effect	Reference
Allopathic medications	Amiodarone	Antiarrhythmic	Inhibition of hepatic metabolism		[78]
	Ciprofloxacin	Antibiotic	Reduction of vitamin K synthesis by intestinal bacteria	Increased bleeding	[79]
	Paroxetine	Antidepressant	Inhibition of hepatic metabolism	Potentiation	[80]
	Citalopram	Antidepressant	Inhibition of hepatic metabolism	Potentiation	[80]
	Clopidogrel	Antiplatelet medication	Inhibition of coagulation cascade	Potentiation	[81]
	Dipyridamole	Antiplatelet medication	Inhibition of coagulation cascade	Potentiation	[81]
	Diclofenac	NSAID	Inhibition of coagulation cascade	Potentiation	[82]
	Naproxen	NSAID	Inhibition of coagulation cascade	Potentiation	[82]
	Acetaminophen	Analgesic	Interference with hepatic metabolism	Increased bleeding	[83]
Food supplements	Fish oil	Lipid profile improvement	Inhibition of coagulation cascade?	Potentiation	[84]
	Pomegranate juice	Antioxidant	Interference with hepatic metabolism	Potentiation	[85]
	Glucosamine	Cartilage improvement	Unknown	Potentiation	[86]
Traditional medications	Chamomile	Medicinal herbal tea	Unknown	Increased bleeding	[87]
	Ginseng	Improving cognitive functions	Unknown	Inhibition	[88]
	St John's wort	Against depression	Induction of metabolism	Inhibition	[89]

Table 1.
Brief overview of possible interactions with warfarin.

transport, delivery, and elimination of warfarin as well as the external availability of vitamin K are potential sites of interaction with other drugs and with food and dietary supplements.

Drugs and food that influence the enterohepatic circulation can all affect the absorption of warfarin. Examples of these are the drug cholestyramine [37] and the avocado fruit [70], which prevent the reabsorption of warfarin in the intestines Concomitant administration of other protein-bound drugs may lead to greater amounts of circulating warfarin and increased risks of bleeding. Valproate sodium increases the bioavailability of warfarin through dislocation of its protein-binding sites [71]. Interference with the metabolism of warfarin is a potential of most drugs that are eliminated by hepatic metabolism. Among these are aspirin [72], non-steroidal anti-inflammatory drugs [72], serotonin reuptake inhibitors [49], anti-platelet agents and some antibiotics [72]. It can go both ways with the metabolism. Induction of the cytochromes will increase the elimination, while occupation of the binding sites by the drugs will increase the availability of warfarin.

Since warfarin acts through elimination of available bioactive vitamin K, variations of the net intake of this vitamin will certainly interfere with the drug action. A high intake of the vitamin will keep the coagulant factors at a higher level and thus inhibit the anticoagulant activity. Likewise, a lower intake will potentiate the effect of warfarin. The vitamin occurs in food in the form of phylloquinone and menaquinone. Phylloquinone is the form mostly found in plants and is also the most abundant form in food [73]. Menaquinones are mainly the product of bacterial production or conversion [74]. Consequently, simple multivitamin and other supplements, food with high vitamin K content [74] as well as antibiotics are sources of fluctuation in vitamin K intake since intestinal bacteria significantly contribute to the production of menaquinones [75].

Recently, another source of interference came into focus. In addition to the previous mentioned parameters, genetic variation in the expression of cytochrome P450 seems to play a role in the metabolism of warfarin [76], thus influencing the availability of the drug [77]. All these considerations make it clear that close monitoring of the individual coagulation ability is necessary for a successful therapy with this agent.

The abovementioned interactions are just a few of the many that are possible. **Table 1** gives examples of a variety of interactions with drugs, food, natural products, and supplements. This is only to underscore the cautious approach patients should practice when taking warfarin.

8. Future prospects and conclusion

Today, coumarins find their application predominantly as anticoagulants in medicine. The narrow therapeutic index of warfarin and related compounds sometimes limit their applicability and consequently there is a constant search for more safe agents in this drug class [90]. Unfortunately, the development of these will probably limit the use of these oral anticoagulants.

Aside from these developments, coumarins with several applications in medical practice are progressively being introduced. Investigators found that coumarin-3-carboxylic acid could be utilized as a dosimeter for radiotherapy. This substance converts to the highly fluorescent 7-hydroxy-coumarin-3-carboxylic acid, with a near perfect linear correlation upon irradiation [91].

The coumarin 2-hydroxycinnamic acid demonstrated inhibitive properties on the enzyme carbonic anhydrase [92]. Inhibition of this enzyme leads to diuresis [93] and decreases intraocular pressure in glaucoma patients [93] with clear therapeutic potential and clinical perspective.

Furano(pyrano)coumarins found in the roots of the Korean angelica (*Angelica gigas*) showed antibacterial activity in hay bacillus (*Bacillus subtilis*) cultures [94]. The coumarine derivative cloricromene reduced the inflammatory parameters in rats subjected to collagen-induced arthritis [95]. In addition, several studies found that coumarins may be useful as anti-tumor agents [4, 96].

Probably since ancient times, coumarins found their application in medicine. Currently, however, coumarins with predominantly anticoagulant properties are applied in daily medical practice. These have been developed from the initial discovery of a cattle killing weed more than six decades ago. Initially applied as a rodenticide, soon a therapeutic usable oral anticoagulant was developed, and slowly other agents entered the market. They have a small therapeutic index, rendering them toxic in a number of circumstances. The search for more safe agents with anticoagulant effects is ongoing and this may result in a decline of the use of coumarins in this field. Nevertheless, coumarins gradually find their way in other fields of medicine. Nevertheless, all these developments promise a bright future for coumarins in medical applications.

Conflict of interest

The author declares no conflict of interest.

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