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Coumarin: Synthesis of Derivative and Its Applications as Antioxidant

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ABSTRACT: The study of coumarin dates back to 1820 when coumarin was first extracted from tonka bean by Vogel. Compounds containing coumarin backbone are a very important group of compounds due to their usage in pharmacy and medicine. Properties and biological activities of coumarin derivatives have a significant role in the development of new drugs. Therefore, many different methods and techniques are developed in order to synthesize coumarin derivatives. Coumarin derivatives could be obtained from different starting materials with various methods but with big differences in yield. Chemically, coumarins (2H-1-benzopyran-2-one) belong to the subgroup of lactones .Coumarin is also known as 1,2-benzopyrone or o-hydroxycinnamic acid-8-lactone .Natural coumarins can be divided into six basic groups as follows: simple coumarins, furanocoumarins, pyrano coumarins (linear type and angular type), dihydrofurano coumarins, phenyl coumarins and bicoumarins .First isolated parent coumarin was from tonka bean in (Dipteryx odorata) 1820 by Vogel.The coumarins name originates from French word “Coumarou” for the tonka bean .

KEYWORDS: coumarin, derivatives, compounds, lactones, tonka bean, pharmacy, medicine

I. INTRODUCTION

Coumarin (2H-1-benzopyran-2-one) and its heterocyclic derivatives are widely used as lactone scaffolds used by innovative methods for the preparation of heterocyclic molecules. Nowadays, significant biological activities, as well as properties of unique nature coumarin derivatives, have played an important role in the development of novel drugs. This chapter entitles numerous methods of one-pot construction of coumarin derivatives, together with well-known name reactions and other type reactions as well, in the presence of various metal-based homogenous and heterogeneous catalyst system. Coumarin is one of the very important heterocycles and its analogs like natural product and pharmaceutically active drug molecules are extracted/isolated from a plants, animals, and microbes.[1] Coumarin precursors have a wide range of biological activities Hence, the synthesis of coumarins and their heterocyclic analogs have become among the most interesting compound over the last many years in the growth of improved synthetic methodologies to form different types of functional groups that are present in coumarins derivatives.[2] The synthesis of coumarins enabled by current approaches and their most recent bio-applications are discussed in this book chapter. Corresponding complex heterocycles-based coumarin analogs are produced from substituted alkyne substrates and other starting materials as well. Coumarin derivatives have a myriad of applications in medical science, biomedical research, and many industrial branches. For this reason, many efforts are being dedicated to the development of novel and more practical methods for synthesizing these compounds. This chapter describes several methods of one-pot synthesis of coumarin derivatives, including von Pechmann condensation,[3] Knoevenagel condensation, Baylis-Hillman reaction, Michael addition, Kostanecki reaction, vinyl phosphonium salt-mediated electrophilic reaction, and Heck-lactonization reaction. This review is a compilation of the green synthetic methods used in the synthesis of coumarin derivatives. Coumarins are a class of compounds with a pronounced wide range of biological activities, which have found their application in medicine, pharmacology, cosmetics and food industry. Their biological activity and potential application are highly dependent on their structure. Therefore, many researchers have been performing the synthesis of coumarin derivatives on a daily basis[4]. High demands for their synthesis often result in an increased generation of different waste chemicals. In order to minimize the utilization and generation of toxic organic substances, green synthetic methods are applied in this manner. These methods are getting more attention in the last few decades. Green chemistry methods cover a wide range of methods, including the application of ultrasound and microwaves, ionic liquids and deep eutectic solvents, solvent-free synthesis, mechanosynthesis and multicomponent reactions. All typical condensation reactions for coumarin synthesis like Knoevenagel, Perkin, Kostanecki-Robinson, Pechmann and Reformansky reactions[5], have been successfully performed using these green synthetic methods. According to the

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authors mentioned in this review, not only these methods reduce the utilization and generation of toxic chemicals, but they can also enhance the reaction performance in terms of product yields, purity, energy consumption and post-synthetic procedures when compared to the conventional methods. Due to the significance of coumarins as biologically active systems and the recent demands of reducing toxic solvents, catalysts and energy consumption,[6] this review provides a first full literature overview on the application of green synthetic methods in the coumarin synthesis. It covers a literature search over the period from 1995-2019. The importance of this work is its comprehensive literature survey on a specific class of heterocyclic compounds, and those researchers working on the coumarin synthesis can find very useful information on the green synthetic approaches to their synthesis. [7]

Coumarin and its derivatives are all considered phenylpropanoids.[11]

Some naturally occurring coumarin derivatives include umbelliferone (7-hydroxycoumarin), aesculetin (6,7-dihydroxycoumarin), herniarin (7-methoxycoumarin), psoralen and imperatorin.[8]

4-Phenylcoumarin is the backbone of the neoflavones, a type of neoflavonoids.

Coumarin pyrazole hybrids have been synthesized from hydrazones, carbazones and thiocarbazones via Vilsmeier Haack formylation reaction.

Compounds derived from coumarin are also called coumarins or coumarinoids; this family includes:

- brodifacoum[22][23]
- bromadiolone[24]
- difenacoum[25]
- auraptene
- ensaculin
- phenprocoumon (Marcoumar)
- PSB-SB-487
- PSB-SB-1202
- Scopoletin can be isolated from the bark of *Shorea pinanga*[9]
- warfarin (Coumadin)

Coumarin is transformed into the natural anticoagulant dicoumarol by a number of species of fungi. This occurs as the result of the production of 4-hydroxycoumarin, then further (in the presence of naturally occurring formaldehyde) into the actual anticoagulant dicoumarol, a fermentation product and mycotoxin. Dicoumarol was responsible for the bleeding disease known historically as "sweet clover disease" in cattle eating moldy sweet clover silage. In basic research, preliminary evidence exists for coumarin having various biological activities, including anti-inflammatory, anti-tumor, antibacterial, and antifungal properties, among others. [10]

II. DISCUSSION

Brodifacoum is a highly lethal 4-hydroxycoumarin vitamin K antagonist anticoagulant poison. In recent years, it has become one of the world's most widely used pesticides. It is typically used as a rodenticide, but is also used to control larger pests such as possum.[2]

Brodifacoum has an especially long half-life in the body, which ranges up to nine months, requiring prolonged treatment with antidotal vitamin K for both human and pet poisonings. It has one of the highest risks of secondary poisoning to both mammals and birds.[3] Significant experience in brodifacoum poisonings has been gained in many human cases where it has been used in attempted suicides, necessitating long periods of vitamin K treatment. In March 2018, cases of severe coagulopathy and bleeding associated with synthetic cannabinoid use contaminated with brodifacoum were reported in five states of the US.[11]

Bromadiolone is a potent anticoagulant rodenticide. It is a second-generation 4-hydroxycoumarin derivative and vitamin K antagonist, often called a "super-warfarin" for its added potency and tendency to accumulate in the liver

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of the poisoned organism. When first introduced to the UK market in 1980, it was effective against rodent populations that had become resistant to first generation anticoagulants.[12]

The product may be used both indoors and outdoors for rats and mice.

It is classified as an extremely hazardous substance in the United States as defined in Section 302 of the Emergency Planning and Community Right-to-Know Act (42 U.S.C. 11002), and is subject to strict reporting requirements by facilities which produce, store, or use it in significant quantities.[1]

Difenacoum is an anticoagulant of the 4-hydroxycoumarin vitamin K antagonist type. It has anticoagulant effects and is used commercially as a rodenticide. It was first introduced in 1976 and first registered in the USA in 2007.[1] Auraptene is a natural bioactive monoterpene coumarin ether. It was first isolated from members of the genus Citrus.

Auraptene has shown some effect as a chemopreventative agent against cancers of liver, skin, tongue, esophagus, and colon in rodent models.[1] Ensaculin (KA-672) is a drug from the coumarin family, which has been researched as a potential treatment for dementia. It acts on a number of receptor systems, being both a weak NMDA antagonist and a $5HT_{1A}$ agonist.[1][2] Animal studies have shown promising nootropic effects,[3][4] although efficacy in humans has yet to be proven. It was well tolerated in human trials, with the main side effect being orthostatic hypotension (low blood pressure).[5] Phenprocoumon (marketed under the brand names Marcoumar, Marcumar and Falithrom)[13] is a long-acting blood thinner drug to be taken by mouth, and a derivative of coumarin.[2] It acts as a vitamin K antagonist and inhibits blood clotting (coagulation) by blocking synthesis of coagulation factors II, VII, IX and X. It is used for the prophylaxis and treatment of thromboembolic disorders such as heart attacks and pulmonary (lung) embolism. The most common adverse effect is bleeding. The drug interacts with a large number of other medications, including aspirin and St John's Wort. It is the standard coumarin used in Germany,[3] Austria,[4] and other European countries.[5] PSB-SB-487 is a coumarin derivative which is an antagonist at the former orphan receptor GPR55. Unlike older GPR55 antagonists such as O-1918, PSB-SB-487 has good selectivity over the related receptor GPR18, with an IC_{50} of 113nM at GPR55 vs 12500nM at GPR18.[1] However it has poorer selectivity over other related receptors, acting as a weak antagonist at CB_1 with a Ki of 1170nM, and a partial agonist at CB_2 with a Ki of 292nM.[2] PSB-SB-1202 is a coumarin derivative which is an agonist at the cannabinoid receptors CB_1 and CB_2, with a CB_1 Ki of 32nM and a CB_2 Ki of 49nM.[1] It is also a weak antagonist at the related receptor GPR55, with an IC_{50} of 6350nM, but has no significant affinity for GPR18.[2] Scopoletin is a coumarin found in the root of plants in the genus Scopolia such as Scopolia carniolica and Scopolia japonica, in chicory, in Artemisia scoparia, in the roots and leaves of stinging nettle (Urtica dioica), in the passion flower, in Brunfelsia, in Viburnum prunifolium, in Solanum nigrum,[1] in Datura metel,[2] in Mallotus resinosus,[3] or and in Kleinhovia hospita. It can also be found in fenugreek,[4] vinegar,[5][4] some whiskies or in dandelion coffee. A similar coumarin is scoparone. Scopoletin is highly fluorescent when dissolved in DMSO or water and is regularly used as a fluorimetric assay for the detection of hydrogen peroxide in conjunction with horseradish peroxidase. When oxidized, its fluorescence is strongly suppressed. Warfarin is an anticoagulant used as a medication under several brand names including Coumadin,[8] and as a poison for rats and other pests.[9][10] While the drug is described as a "blood thinner", it does not reduce viscosity but inhibits coagulation, and is commonly used to prevent blood clots in the circulatory system such as deep vein thrombosis and pulmonary embolism, and to protect against stroke in people who have atrial fibrillation, valvular heart disease, or artificial heart valves.[8] Less commonly, it is used following ST-segment elevation myocardial infarction and orthopedic surgery.[8] It is usually taken by mouth, but may also be administered intravenously.[8]

The common side effect, a natural consequence of reduced clotting, is bleeding.[8] Less common side effects may include areas of tissue damage, and purple toes syndrome.[8] Use is not recommended during pregnancy.[8] The effects of warfarin are typically monitored by checking prothrombin time (INR) every one to four weeks.[8] Many other medications and dietary factors can interact with warfarin, either increasing or decreasing its effectiveness.[8][11] The effects of warfarin may be reversed with phytomenadione (vitamin K_1), fresh frozen plasma, or prothrombin complex concentrate.[11]

Warfarin decreases blood clotting by blocking vitamin K epoxide reductase, an enzyme that reactivates vitamin K_1.[11] Without sufficient active vitamin K_1, clotting factors II, VII, IX, and X have decreased clotting ability.[11] The anticlotting protein C and protein S are also inhibited, but to a lesser degree.[11] A few days are required for full effect to occur, and these effects can last for up to five days.[8][12] Because the mechanism involves enzymes such as VKORC1,

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patients on warfarin with polymorphisms of the enzymes may require adjustments in therapy if the genetic variant that they have is more readily inhibited by warfarin, thus requiring lower doses.[13][14]

Warfarin first came into large-scale commercial use in 1948 as a rat poison.[15][9] It was formally approved as a medication to treat blood clots in humans by the U.S. Food and Drug Administration in 1954.[8] In 1955, warfarin's reputation as a safe and acceptable treatment was bolstered when President Dwight D. Eisenhower was treated with warfarin following a massive and highly publicized heart attack.[16] Eisenhower's treatment kickstarted a transformation in medicine whereby coronary artery disease, arterial plaques, and ischemic strokes were treated and protected against by using anticoagulants such as warfarin. It is on the World Health Organization's List of Essential Medicines.[17][18] Warfarin is available as a generic medication[19] and under many trade names.[1] In 2020, it was the 58th most commonly prescribed medication in the United States, with more than 11 million prescriptions.[20][21]

III. RESULTS

Brodifacoum is a derivative of the 4-hydroxy-coumarin group. Compounds numbers are found next to their respective compounds in the image below. Compound 1 is the starting ester needed to synthesize brodifacoum. To obtain this starting Compound 1, a simple Wittig condensation of ethyl chloroacetate with 4'-bromobiphenylcarboxaldehyde is accomplished. Compound 1 is transformed into Compound 2 by consecutive hydrolysis[14], halogenation to form an acid chloride, and then reacted with the required lithium anion. This is done using KOH and EtOH for hydrolysis, and then adding $SOCl_2$ for chlorination to form the acid chloride which reacts with the addition of lithium anion. Compound 2 is then transformed using organocopper chemistry to yield Compound 3 with good stereoselectivity of about 98%. Typically, a Friedel-Crafts type cyclization would then be used to obtain the two-ring system portion of Compound 4, but this results in low yield. Instead, trifluoromethanesulfonic acid in dry benzene catalyzes the cyclization with good yield. The ketone is then reduced with sodium borohydride yielding a benzyl alcohol[15]. Condensation with 4-hydroxycoumarin under HCl yields Compound 5, brodifacoum.[4] Bromadiolone can be absorbed through the digestive tract, through the lungs, or through skin contact. The pesticide is generally given orally.[2] The substance is a vitamin K antagonist. The lack of vitamin K in the circulatory system reduces blood clotting and will cause death due to internal hemorrhaging.[2]

Poisoning does not show effects for 24 to 36 hours after it is eaten and can take up to 2–5 days to cause death.

Following are acute LD_{50} values for various animals (mammals):[2]

- rats 1.125 mg/kg b.w.
- mice 1.75 mg/kg b.w.
- rabbits 1 mg/kg b.w.
- dogs > 10 mg/kg b.w. (oral MTD)[3]
- cats > 25 mg/kg b.w. (oral MTD)[3]

Because other species of mammals and birds may prey upon affected rodents, or directly ingest rodenticide bait, there is a risk of primary, secondary or tertiary exposure; examples are described in a 2012 publication on veterinary toxicology.[3] Using radiolabeled isotopes, difenacoum (and/or its metabolites) has been shown to be distributed across many organ tissues upon oral ingestion, with the highest concentrations occurring in the liver [16]and pancreas.Difenacoum has been shown to be highly toxic to some species of freshwater fish and green algae despite the fact that difenacoum is weakly soluble in aqueous solutions. Phenprocoumon is an inhibitor of the enzyme vitamin K epoxide reductase (VKOR). Vitamin K is needed to activate the coagulation factors II, VII, IX and X[9] and the anticoagulation factors protein C and protein S,[10] in which process it turns into vitamin K 2,3-epoxide. This is then recycled to vitamin K in a process involving VKOR. Inhibiting this enzyme effectively creates a vitamin K deficiency, [17] blocking activation of the coagulation factors. After 36 to 72 hours, the available activated factors have been depleted (used up) by the coagulation system, and the anticoagulation takes effect.[1]

Like most phenylpropanoids, the biosynthetic precursor to scopoletin acid is 4-coumaroyl-CoA.[6] Scopoletin is derived from 1,2-benzopyrones[7] which is the core structure of coumarins formed through hydroxylation of cinnamates,

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trans/cis isomerization of the side chain, and lactonization.[8] And CYP98A (C3'H) are enzymes belonging to the cytochrome P450 family that catalyze the meta-hydroxylation of p-coumarate derivatives, an important step in the phenylpropanoid pathway.[9] For scopoletin, most of biosynthetic investigations are based on Arabidopsis thaliana.

Warfarin – a coumarin – with brand name, Coumadin, is a prescription drug used as an anticoagulant to inhibit formation of blood clots, and so is a therapy for deep vein thrombosis and pulmonary embolism. It may be used to prevent recurrent blood clot formation from atrial fibrillation, thrombotic stroke, and transient ischemic attacks[18].

Coumarins have shown some evidence of biological activity and have limited approval for few medical uses as pharmaceuticals, such as in the treatment of lymphedema. Both coumarin and 1,3-indandione derivatives produce a uricosuric effect, presumably by interfering with the renal tubular reabsorption of urate.[31] Coumarin is used in the pharmaceutical industry as a precursor reagent in the synthesis of a number of synthetic anticoagulant pharmaceuticals similar to dicoumarol.[1] 4-hydroxycoumarins are a type of vitamin K antagonist.[1] They block the regeneration and recycling of vitamin K. These chemicals are sometimes also incorrectly referred to as "coumadins" rather than 4-hydroxycoumarins. Some of the 4-hydroxycoumarin anticoagulant class of chemicals are designed to have high potency and long residence times in the body, and these are used specifically as rodenticides ("rat poison").[1] Death occurs after a period of several days to two weeks, usually from internal hemorrhaging. Coumarin is often found in artificial vanilla substitutes, despite having been banned as a food additive in numerous countries since the mid-20th century. It is still used as a legal flavorant in soaps, rubber products, and the tobacco industry,[1] particularly for sweet pipe tobacco and certain alcoholic drinks.[19]

Coumarin is moderately toxic to the liver and kidneys of rodents, with a median lethal dose (LD_{50}) of 293 mg/kg in the rat a low toxicity compared to related compounds. Coumarin is hepatotoxic in rats, but less so in mice. Rodents metabolize it mostly to 3,4-coumarin epoxide, a toxic, unstable compound that on further differential metabolism may cause liver cancer in rats and lung tumors in mice. Humans metabolize it mainly to 7-hydroxycoumarin, a compound of lower toxicity, and no adverse affect has been directly measured in humans. The German Federal Institute for Risk Assessment has established a tolerable daily intake (TDI) of 0.1 mg coumarin per kg body weight, but also advises that higher intake for a short time is not dangerous The Occupational Safety and Health Administration (OSHA) of the United States does not classify coumarin as a carcinogen for humans. [21]

European health agencies have warned against consuming high amounts of cassia bark, one of the four main species of cinnamon, because of its coumarin content. According to the German Federal Institute for Risk Assessment (BFR), 1 kg of (cassia) cinnamon powder contains about 2.1 to 4.4 g of coumarin. Powdered cassia cinnamon weighs 0.56 g/cm^3. so a kilogram of cassia cinnamon powder equals 362.29 teaspoons. One teaspoon of cassia cinnamon powder therefore contains 5.8 to 12.1 mg of coumarin, which may be above the tolerable daily intake value for smaller individuals. However, the BFR only cautions against high daily intake of foods containing coumarin. Its report specifically states that Ceylon cinnamon (Cinnamomum verum) contains "hardly any" coumarin.[22]

The European Regulation (EC) No 1334/2008 describes the following maximum limits for coumarin: 50 mg/kg in traditional and/or seasonal bakery ware containing a reference to cinnamon in the labeling, 20 mg/kg in breakfast cereals including muesli, 15 mg/kg in fine bakery ware, with the exception of traditional and/or seasonal bakery ware containing a reference to cinnamon in the labeling, and 5 mg/kg in desserts.

An investigation from the Danish Veterinary and Food Administration in 2013 shows that bakery goods characterized as fine bakery ware exceeds the European limit (15 mg/kg) in almost 50% of the cases. The paper also mentions tea as an additional important contributor to the overall coumarin intake, especially for children with a sweet habit.[23]

Coumarin was banned as a food additive in the United States in 1954, largely because of the hepatotoxicity results in rodents. Coumarin is currently listed by the Food and Drug Administration (FDA) of the United States among "Substances Generally Prohibited From Direct Addition or Use as Human Food," according to 21 CFR 189.130, but some natural additives containing coumarin, such as the flavorant sweet woodruff are allowed "in alcoholic beverages only" under 21 CFR 172.510. In Europe, popular examples of such beverages are Maiwein, white wine with woodruff, and Żubrówka, vodka flavoured with bison grass.

Coumarin is subject to restrictions on its use in perfumery, as some people may become sensitized to it, however the evidence that coumarin can cause an allergic reaction in humans is disputed. [24]

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Minor neurological dysfunction was found in children exposed to the anticoagulants acenocoumarol or phenprocoumon during pregnancy. A group of 306 children were tested at ages 7–15 years to determine subtle neurological effects from anticoagulant exposure. Results showed a dose–response relationship between anticoagulant exposure and minor neurological dysfunction. Overall, a 1.9 (90%) increase in minor neurological dysfunction was observed for children exposed to these anticoagulants, which are collectively referred to as "coumarins." In conclusion, researchers stated, "The results suggest that coumarins have an influence on the development of the brain which can lead to mild neurologic dysfunctions in children of school age." [25]

Coumarin's presence in cigarette tobacco caused Brown & Williamson executive Dr. Jeffrey Wigand to contact CBS's news show 60 Minutes in 1995, charging that a “form of rat poison” was in the tobacco. He held that from a chemist’s point of view, coumarin is an “immediate precursor” to the rodenticide coumadin. Dr. Wigand later stated that coumarin itself is dangerous, pointing out that the FDA had banned its addition to human food in 1954. Under his later testimony, he would repeatedly classify coumarin as a "lung-specific carcinogen." In Germany, coumarin is banned as an additive in tobacco.[23]

Alcoholic beverages sold in the European Union are limited to a maximum of 10 mg/L coumarin by law. Cinnamon flavor is generally cassia bark steam-distilled to concentrate the cinnamaldehyde, for example, to about 93%. Clear cinnamon-flavored alcoholic beverages generally test negative for coumarin, but if whole cassia bark is used to make mulled wine, then coumarin shows up at significant levels.

IV. CONCLUSIONS

Brodifacoum is a 4-hydroxycoumarin anticoagulant, with a similar mode of action to its historical predecessors dicoumarol and warfarin. However, due to very high potency and long duration of action (elimination half-life of 20 – 130 days), it is characterised as a "second-generation" or "superwarfarin" anticoagulant.[5]

Brodifacoum inhibits the enzyme vitamin K epoxide reductase, which is needed for the reconstitution of the vitamin K in its cycle from vitamin K-epoxide, so brodifacoum steadily decreases the level of active vitamin K in the blood. Vitamin K is required for the synthesis of important substances including prothrombin, which is involved in blood clotting. This disruption becomes increasingly severe until the blood effectively loses any ability to clot.[20]

In addition, brodifacoum (as with other anticoagulants in toxic doses) increases permeability of blood capillaries; the blood plasma and blood itself begin to leak from the smallest blood vessels. A poisoned animal suffers progressively worsening internal bleeding, leading to shock, loss of consciousness, and eventually death. Difenacoum was first introduced in 1976 as a rodenticide effective against rats and mice which were resistant to other anticoagulants.[2] Phenprocoumon is used for the prophylaxis and treatment of thromboembolic disorders after heart bypass surgery and myocardial infarction (heart attack), long-term treatment of myocardial infarction with increased risk of thromboembolism, thrombophilia (abnormal blood clotting), antithrombin III deficiency, atrial fibrillation (a kind of abnormal heart rhythm) with artery embolisms, after venous thrombosis, pulmonary embolism and artificial heart valve surgery, as well as chronic ventricular aneurysm (bulging of the heart wall) and congestive cardiomyopathy (enlarged heart).[1] Warfarin is used to decrease the tendency for thrombosis, or as secondary prophylaxis (prevention of further episodes) in those individuals who have already formed a blood clot (thrombus). Warfarin treatment can help prevent formation of future blood clots and help reduce the risk of embolism (migration of a thrombus to a spot where it blocks blood supply to a vital organ).[22]

Warfarin is best suited for anticoagulation (clot formation inhibition) in areas of slowly running blood (such as in veins and the pooled blood behind artificial and natural valves), and in blood pooled in dysfunctional cardiac atria. Thus, common clinical indications for warfarin use are atrial fibrillation, the presence of artificial heart valves, deep venous thrombosis, and pulmonary embolism (where the embolized clots first form in veins). Warfarin is also used in antiphospholipid syndrome.[24] It has been used occasionally after heart attacks (myocardial infarctions), but is far less effective at preventing new thromboses in coronary arteries. Prevention of clotting in arteries is usually undertaken with antiplatelet drugs, which act by a different mechanism from warfarin (which normally has no effect on platelet function).[23] It can be used to treat people following ischemic strokes due to atrial fibrillation, though direct oral anticoagulants (DOACs) may offer greater benefits.[25]

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