Plant Coumarins

Myths and Realities

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Abstract

Plant coumarins are structurally distinct, nonanticoagulant compounds that have significant medical activity. They can be fermented by various fungi to metabolites, which then dimerize to vitamin K–antagonist anticoagulants, but these are not inherently found in any known plants. Plant coumarins are often described as being anticoagulant and as interacting with drug anticoagulants, despite all evidence to the contrary. Coumarin itself does have potential to cause hepatotoxicity, perhaps in the tiny subset of people who take enough and have insufficient CYP2A6 activity to break coumarin down into safe catabolites. The particular concern over *Cinnamomum aromaticum* (cassia) versus *Cinnamomum zeylanicum* (true cinnamon) is discussed. Plant coumarins and plants rich in these compounds, including *Melilotus* spp. (sweet clover), *Angelica keiskei* (*ashitaba*), *Angelica pubescens* (pubescent angelica), *Artemisia scoparia* (*yin-chen* wormwood), *Citrus* spp. (orange), *Glycyrrhiza uralensis* (licorice), *Justicia pectoralis* (chambá), *Mikania glomerata* (*guaco*), *Pelargonium sidoides* (African geranium), and *Leonurus heterophyllus* (Chinese motherwort), have demonstrated inflammation-modulating, antiedema, and anticancer activities. The time is long past to stop looking at these compounds as anticoagulants and instead focus on the true benefits and potential harms associated with them.

Introduction

Many sources of information suggest that coumarin has anticoagulant activity and that herbal medicines containing coumarin may therefore interact with anticoagulant drugs. These statements are generally given as fact with no supporting references cited. In fact, peer-reviewed medical journal papers sometimes carelessly substitute the word coumarin when they actually mean warfarin, phenprocoumon, or other synthetic coumarin-derived but distinct drugs.[1] Besides being technically incorrect, this creates confusion and propagates a myth about plant coumarins being anticoagulant.

The story of how coumarin-containing herbs came to be seen as identical to metabolites formed when those herbs were fermented or ingested by ruminants, and even how they came to be equated with synthetic agents made from those metabolites, is instructive in how the pharmacologic model distorts and confuses herbal medicine. After revealing and dispelling myths about coumarins and the clotting system, the real actions and potential hazards of endogenous plant coumarins is discussed.

The Coumarin Anticoagulant Myth

In the twentieth century and possibly before, it was known that cattle sometimes died of spontaneous bleeding.[2] Francis Schofield, a British émigré to Canada, investigated the problem and in 1922 determined that moldy *Melilotus* spp. (sweet clover) was the culprit. Researchers Karl Link and Harold Campbell at the University of Wisconsin studied the chemical basis of the problem and identified it as dicoumarol, formed ultimately from coumarin in the sweet clover.[3] Coumarin is converted to 4-hydroxycoumarin by several genera of fungi (*Penicillium*, *Aspergillus*, *Fusarium*, and *Mucor* among others), which can then spontaneously dimerize to dicoumarol.[4] Link and Campbell synthesized many variants of dicoumarol, eventually hitting upon a molecule they named warfarin (after their funding agency, the Wisconsin Alumni Research Fund). This molecule was eventually given the highly confusing trade name of Coumadin.™

Manifestly, coumarin is not dicoumarol or Coumadin (see Table 1 for nomenclature and structures of coumarin compounds). They are structurally and physiologically distinct. To say that coumarin has the same actions as dicoumarol or warfarin based simply on molecular structure and precursor status is not rational. Instead, one must investigate whether coumarin itself has effects on the vitamin K–related clotting system.

At least one clinical trial has been conducted looking at the question of whether actual coumarin affects blood clotting.[5] In a randomized trial, 20 patients already being treated for venous insufficiency with 90 mg of coumarin daily (along with a synthetic flavonoid, troxerutin) and 21 patients in the control group being treated with benzarone (another agent for edema) were given a broad assessment of coagulation status. They had been taking the medicines for 6 weeks prior to being tested. There was no evidence of any change in any coagulation parameter, including clotting factor- and fibrin-related processes. While obviously this was not a very large study, it is the only study located by the authors to date looking directly at the question, and it does not support that even relatively high doses of oral, natural coumarin are anticoagulant.

Animal studies are also scanty in terms of evaluating whether natural coumarins in plants are anticoagulant. One study looked at an extract of the herb *Pelargonium sidoides* (African geranium), which contains substantial levels of natural coumarins, in rats.[6] Even at doses as high as 500 mg/kg for 2 weeks, there was no effect on any coagulation parameter in the rats. Rats pretreated with African geranium extract at similar doses simultaneously given warfarin also developed no changes in warfarin activity.

Coumarin analogs, including some found in plants, may have anticoagulant effects, but much work remains to be done to prove this.

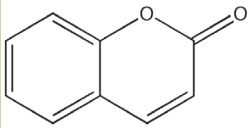
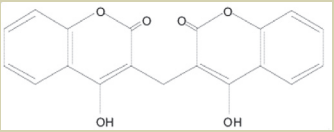
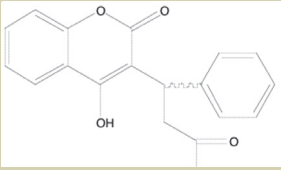
For example, *Leonurus heterophyllus* (Chinese motherwort, *yi mu cao*) has been used as a "blood mover" in Oriental medicine An open clinical trial in 105 patients showed that intravenous (IV) injections of an extract of Chinese motherwort could decrease blood viscosity, decrease fibrinogen, and inhibit platelet aggregation.[7] Chinese motherwort does contain the coumarin-derivative prehispanolone, which, in vitro, has been shown to act as a platelet activating factor receptor antagonist.[8] Even if we set aside the dubious idea of extrapolating from a study of IV injections to oral dosing of the same herb, this is still far from proof that an herbal extract containing a coumarin derivative, taken at usual doses orally, has vitamin K–antagonist anticoagulant properties.

Matricaria recutita (chamomile).

The Coumarin Did It

Often coumarin or coumarin-like constituents in plants are blamed when there is any report of bleeding or interactions with anticoagulant drugs related to plants in the literature. For example, a case study has been published of an association between drinking *Matricaria recutita* (chamomile,

Table 1. Coumarin Terminology

Main term	Synonyms	Chemical structure
Coumarin	1-benzopyran-2-one	
Bishydroxycoumarin	dicoumarol, 3,3′-methylene-*bis*-(4-hydroxycoumarin), Dicoumarol,™ Dicumarol,™ nicoumalone	
Warfarin	Coumadin,™ S-warfarin, R-warfarin	

Ruscus aculeatus (butcher's broom). Drawing by Kathy Abascal, B.S., J.D., R.H. (AHG), 2009.

formerly known as *Matricaria chamomilla*) tea and internal bleeding in a 70-year-old woman taking warfarin and many other medications.[9] The authors stated that since she had been on her medications for 3 years, there was no chance of a drug–drug interaction, apparently forgetting that individual biology can change over time and interactions can develop at any point during use. The authors confusingly wrote: "Although no evidence of a drug–herb interaction between warfarin and *M. chamomilla* has been documented, there is a theoretical risk because it is thought to be a coumarin constituent." The whole herb is not a "constituent," but a combination of many hundreds of constituents.

Claiming that, because one coumarin-derived family of molecules is anticoagulant, all coumarins are anticoagulant is bad science.

In any case, the patient apparently took 4–5 tsp of chamomile herb in tea (to self-treat a respiratory infection) along with 1–2 applications of chamomile-containing cream on her legs 4–5 times per day (to self-treat pedal edema) for a few days before the bleeding occurred. The authors report that she also used a "camphor-based lotion" on her chest to self-treat the respiratory infection as well, yet never hypothesize that this agent may have interacted with her warfarin. It is very possible this lotion contained methyl salicylate, and, unlike the completely theoretical chamomile connection, there is documentation in the literature of topical methyl salicylate interacting negatively with warfarin in humans.[10–12]

Though more research is needed on this topic as well, it makes the authors of this case study's thesis that chamomile was to blame highly suspect, and coumarin-related compounds in chamomile being the culprit even more unlikely. Still, the case study oddly stated that "[c]hamomile's propensity to cause anticoagulation has been known, but no instance of interaction been reported." How can such anticoagulative powers be known with no reported instances of such an effect?

The baseless simplification that, because one coumarin-derived family of molecules (warfarin, dicoumarol) is anticoagulant, all coumarins must be anticoagulant is bad science and bad thinking. In order to have anticoagulant activity, coumarin-based molecules have certain structural requirements, although those requirements are absent from most documented nonmoldy plant coumarins to date, and from coumarin itself. Desai, summarizing work by Link, stated that at a minimum, a coumarin-based molecule must have a 4-hydroxy group and a *bis*-substituent attached at the 3 position to be anticoagulent.[13]

However, now that this case study is in the literature, it can be cited as "proof" that chamomile and its coumarins are anticoagulant. As many people will not read the details of the report and think about the intricacies involved, it will end up being repeatedly mis-cited, furthering the urban myth that plant coumarins are anticoagulant and must be avoided with anticoagulants. The case for this argument has not, in fact, been made. (See Summary of Evidence That Coumarin Is Not Anticoagulant.)

Summary of Evidence That Coumarin Is Not Anticoagulant

1. Coumarin and Coumadin™ (warfarin) have historically been confused because of the unfortunate similarity of their names.
2. The only published human clinical trial of pure coumarin located to date showed no effect on bleeding.
3. Existing animal studies do not support that coumarin is anticoagulant.
4. Coumarin and anticoagulant molecules, such as dicoumarol and warfarin, have been shown to have distinctive structures (and coumarin lacks those elements necessary for anticoagulant activity).

Plant Coumarins for Edema

Coumarin and its many congeners' main benefits lie in supporting connective tissue, modulating inflammation, and reducing edema.[14] In a large clinical trial, 231 subjects with chronic venous insufficiency were initially randomized to take 90 mg of coumarin with 540 mg of the synthetic flavonoid troxerutin or placebo daily for 4 weeks.[15] The subjects were

then crossed over to the opposite treatment, which they maintained for 12 weeks. All subjects used venous compression stockings throughout the trial. During phases in which coumarin and troxerutin were used, edema-related leg volume was significantly reduced compared with the placebo group. No serious adverse effects occurred during the trial.

An attempt at meta-analysis of the several other clinical trials published on using coumarin for patients with lymphedema has so far not been possible due to poor data reporting in these clinical trials.[16]

Two trials on crude plant extracts of the coumarin-rich herb *Melilotus officinalis* (sweet clover) for patients with chronic venous insufficiency have been reported. The first, an open trial, used a topical cream of sweet clover and *Ruscus aculeatus* (butcher's broom) and found it beneficial in most patients.[17] In a controlled clinical trial of 30 patients with chronic venous insufficiency, an oral supplement containing sweet clover, vitamin E, rutin, and *Centella asiatica* (gotu kola) was compared with placebo for 30 days and found superior for reducing edema.[18] Details of these trials, published only in Italian, were not available for analysis.

Many other preclinical studies suggest some of the more than 1300 plant coumarins discovered to date contribute to the inflammation-modulating effects of a range of herbs.[19] See Table 2 for just a handful of examples out of the many that exist, as well as some other miscellaneous actions attributed to plant coumarins.[19]

Plant Coumarins for Cancer

Coumarins have a range of anticancer activities that have led to interest both in natural and synthetic coumarins as potential treatments for people with cancer, as well as potentially preventing cancer.[20]

A number of controlled clinical trials have been reported using pure coumarin to treat patients with advanced cancer, or to attempt to prevent recurrence of resected, serious cancers. For example, 50-mg oral doses of coumarin for 2 years after resection of malignant melanoma led to a significantly lower rate of recurrence of the cancer than placebo in one randomized trial of 27 patients.[21]

Four of 13 (31%) of coumarin-treated versus 10 of 14 (71%) of placebo-treated patients had recurrences at 2 years. This trial was stopped early as a result of this outcome, and all patients were switched to receive coumarin. At least two other groups have failed to find similar results in patients with

Table 2. Miscellaneous Preclinical Research on Coumarins in Herbs

Latin name and part	Common name	Coumarin (if identified)	Action	References
Angelica keiskei stem	Ashitaba	Selindin	Antiallergic	*
Angelica pubescens root	*Du huo*, pubescent angelica	Osthole	Hypotensive, spasmolytic, inflammation-modulating	†–§
Artemisia scoparia leaf	*Yin-chen*, wormwood, *zhu mao hao*	Scoparone	Hypolipidemic, nerve growth stimulant	*¶
Citrus spp. rind	Orange	Auraptene	Anti–*Helicobacter pylori*	‖
Glycyrrhiza uralensis root	*Gan cao*, Chinese lico rice	Glycyrol	Inflammation-modulating	‖
Justicia pectoralis leaf	Chambá	Coumarin, umbelliferone	Inflammation-modulating	‖
Melilotus officinalis herb	White sweet clover	Coumarin (0.25%)	Inflammation-modulating	‖
Melilotus suaveolens herb	*Shinagawa hagi*, *Daghestan*, sweet clover	Coumarin	Inflammation-modulating	§§
Mikania glomerata leaf	Guaco	Coumarin	Bronchodilating	¶¶

*Kishiro S, Nunomura S, Nagai H, et al. Selinidin suppresses IgE-mediated mast cell activation by inhibiting multiple steps of Fc epsilonRI signaling. Biol Pharm Bull 2008;31:442–448; †Hoult JR, Payá M. Pharmacological and biochemical actions of simple coumarins: Natural products with therapeutic potential. Gen Pharmacol 1996;27:713–722; ‡Liu JH, Zschocke S, Reininger E, Bauer R. Inhibitory effects of *Angelica pubescens* F. biserrata on 5-lipoxygenase and cyclooxygenase. Planta Med 1998;64:525–529; §Teng C-M, Lin C-H, Ko F-N, et al. The relaxant action of osthole isolated from *Angelica pubescens* in guinea-pig trachea. N-S Arch Pharmacol 1994;349:202–208; ¶Yang YJ, Lee HJ, Choi DH, et al. Effect of scoparone on neurite outgrowth in PC12 cells. Neurosci Lett 2008;440:14–18; ‖Takeda K, Utsunomiya H, Kakiuchi S, et al. Citrus auraptene reduces *Helicobacter pylori* colonization of glandular stomach lesions in Mongolian gerbils. J Oleo Sci 2007;56:253–260; **Shin EM, Zhou HY, Guo LY, et al. Anti-inflammatory effects of glycyrol isolated from *Glycyrrhiza uralensis* in LPS-stimulated RAW264.7 macrophages. Int Immunopharmacol 2008;8:1524–1532; ††Lino CS, Viana GSB, Matos FJA. Analgesic and antiinflammatory activities of *Justicia pectoralis* Jacq and its constituents: Coumarin and umbeliferone. Phytother Res 1997;11:211–215; ‡‡Plesca-Manea L, Parvu AE, Parvu M, et al. Effects of *Melilotus officinalis* on acute inflammation. Phytother Res 2002;16:316–319; §§Zhao L, Tao JY, Zhang SL, et al. Inner anti-inflammatory mechanisms of petroleum ether extract from *Melilotus suaveolens* Ledeb. Inflammation 2007;30:213–223; ¶¶Soares de Moura R, Costa SS, Jansen JM, Silva CA, et al. Bronchodilator activity of *Mikania glomerata* Sprengel on human bronchi and guinea-pig trachea. J Pharm Pharmacol 2002;54:249–256.

advanced, metastatic melanoma using 100 mg of coumarin daily for 8 weeks followed by adding cimetidine (also previously reported to have antimelanoma effects) 100 mg–1200 mg daily.[22,23] Further trials are warranted to determine the optimal dose of coumarin in patients with melanoma. Coumarin should also be tested in combination with other therapies. It may have a major role to play in preventing recurrence of early stage melanoma.

After administration of up to 7 g of coumarin (which led to nausea and vomiting; 5 g was considered the maximum safe dose), six patients with renal-cell carcinoma experienced objective tumor shrinkage in one preliminary trial.[24] A larger trial with 45 patients who had metastatic renal-cell carcinoma was then attempted, giving the subjects 100 mg of coumarin and 300 mg of cimetidine four times daily (starting day 15 of the study).[25] Some tumors shrank, but the median duration of such response was only 5 months. At most, a small number of patients had disease stabilization for up to 16 months. Sixteen patients had no response. There were no significant adverse effects.

Cheaper cassia, sold as cinnamon, exposes people who cook and bake with cassia to potential coumarin toxicity.

Another group of 50 patients underwent the same protocol, but the coumarin dose was increased to 100 mg four times daily if disease progression occurred.[26] Only 6% of patients showed any response, and 74% (37/50) had mild-to-moderate elevations in serum creatinine levels, suggesting there was some renal toxicity. In one other case series of 38 patients with metastatic renal-cell carcinoma using 100 mg of coumarin with 400 mg of cimetidine daily, there were two complete remissions (lasting 30 and 50 months).[27]

While, clearly, coumarin, at least at the dose tested, is not a very active therapy, it is quite safe. Dose-ranging studies and attempts to combine it with other therapies should be studied to determine if there is a role for coumarin in this very serious disease.

Coumarin and Hepatotoxicity

Isolated coumarin and herbs with high levels of coumarin may be damaging to the liver. Most people metabolize ingested coumarin to 7-hydroxycoumarin and its byproducts. These compounds are nontoxic and are excreted without harm. However, some people, and most rats, have a predominant 3-hydroxylation metabolic pattern or are slow metabolizers, and, in some studies, metabolic fates of coumarin in humans can be highly variable.[28,29] It is well-known that cytochrome 2A6 (CYP2A6) is responsible for 7-hydroxylation of coumarin.[30] People who lack significant CYP2A6 activity may be at increased risk of coumarin hepatotoxicity, and it has been suggested that, when contemplating giving coumarin or coumarin-rich herbs to patients, that they be tested to detect intact CYP2A6 activity before being recommending a prescription, for greatest safety.[31]

Published clinical trials of isolated coumarin have rarely cited hepatotoxicity, supporting the concept that most people are not susceptible to these effects, at least at usual doses. For example, one large trial of 2137 patients with cancer or infections found that 8 (0.37%) developed elevated serum liver enzymes.[32]

In another trial of coumarin and troxerutin for venous insufficiency with 231 subjects lasting 16 weeks, 5% of patients had an elevation of serum liver enzymes compared with 2% in the placebo group.[33] No serious adverse effects occurred. Past history of liver disease was associated with a higher risk of having elevated serum liver enzymes.

In a trial of 140 women postmastectomy with lymphedema, 200 mg of coumarin twice daily was associated with 6% of subjects developing elevated serum liver enzyme levels.[34]

In one rat study, it was shown that troxerutin completely abrogated the hepatotoxicity of coumarin in vitro, though this was seen only at very high doses.[35] Because at least part of the toxicity of coumarin dysmetabolism is formation of 3,4-hydroxycoumarin epoxides, which act like free radicals, antioxidants may help reduce the already-very-low risk of coumarin hepatotoxicity in humans further.

Despite all this, the German Federal Institute for Risk Assessment has set an upper limit of 0.5 mg/kg body weight for coumarin in Germany (for a 170-lb [75-kg] adult man; 37.5 mg of coumarin).[36] Several food ingredients contain sufficient coumarin levels to exceed this intake, most notably *Cinnamomum aromaticum* (cassia) bark. In one detailed analysis, powdered cassia bark contained 1250–1490 mg/kg of coumarin, and its essential oil contained 4370 mg/kg of coumarin.[37] By comparison, *Cinnamomum zeylanicum* (true or Ceylon cinnamon) bark powder had 2.4 mg/kg and its essential oil 40 mg/kg of coumarin.

Much of what is sold as cinnamon in the United States and Europe is now the cheaper cassia, exposing people who cook and bake with cassia to potential coumarin toxicity. Coumarin levels in baked goods using cassia in the previously cited study were often above 50 mg/kg. While the recommended safety levels are lower than doses used with apparent safety in clinical trials, the sheer scale of consumption of cassia in food is so much higher that lower safety thresholds are necessary. *Asperula odorata* (also known as *Galium asperula*, sweet woodruff) and *Dipterix odorata* (tonka bean) are two other flavoring agents with high coumarin levels.

Cassia has recently been reported in clinical trials to improve glucose tolerance in some people with diabetes.[38] A teaspoon of cassia cinnamon powder can contain 5–15 mg of coumarin, which could, if taken three times per day, exceed the German

safety limit and pose a potential hepatotoxicity risk, particularly in people taking cinnamon supplements but actually getting cassia.

Coumarin and coumarin-rich herbs represent a small risk for causing hepatotoxicity. Rather than wasting time assuming or pretending plant coumarins are anticoagulant risks, patients should, instead, be monitored primarily for hepatotoxicity.

Conclusion

Coumarin-rich herbs are generally believed to be anticoagulant, though this has been demonstrated not to be true in various lines of research. Anticoagulant coumarin-derived analogs are structurally and functionally distinct and should be treated as such. Coumarin-rich herbs do represent useful inflammation-modulating, edema-reducing, and possibly anticancer therapies, based on clinical and historical evidence. However, particularly in individuals with low CYP2A6 function, coumarin-rich herbs can lead to an increased risk of hepatotoxicity. ■

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