



HerbClip™

Mariann Garner-Wizard
John Neustadt, ND
Cathleen Rapp, ND

Shari Henson
Heather S Oliff, PhD
Densie Webb, PhD

Brenda Milot, ELS
Marissa Oppel, MS

Executive Editor – Mark Blumenthal

Managing Editor – Lori Glenn

Consulting Editors – Dennis Awang, PhD, Steven Foster, Roberta Lee, MD

Funding/Administration – Wayne Silverman, PhD *Production* – George Solis/Kathleen Coyne

FILE: ■Red Clover (*Trifolium pratense*)
■Coumarins
■Herb-drug Interactions

HC 050155-291

Date: October 31, 2005

RE: Coumarins in Discussion of Herb-drug Interactions

Booth N, Nikolic D, van Breemen R, Geller S, Banuvar S, Shulman L, et. al. Confusion regarding anticoagulant coumarins in dietary supplements. *Clin Pharmacol Ther* 2004;76:511–516.

As the number of people using dietary supplements continues to grow, an increasing amount of research is being conducted to understand actual and potential herb-drug interactions. Coumarins are constituents of plants that are "sometimes confused with the clinical term *coumarins*, which is often used to refer to warfarin (Coumadin; Bristol-Myers Squibb Company, Princeton, NJ) or other specific synthetic anticoagulant drugs." An incomplete understanding of the structure and function of naturally-occurring coumarins causes confusion and concern that plant coumarins will decrease blood clotting and potentiate anticoagulant drug therapies. The goal of the present study was to "educate readers about the differences in biologic activity among the vast pool of naturally occurring coumarins, to present a rational approach for investigation of specific botanicals for coumarins of interest, and to present the chemical analysis of one clinical red clover extract as a case study and discuss preliminary clinical findings regarding patient prothrombin/international normalized ratio (PT/INR) measurements, in support of the hypothesis that the product will not cause blood coagulation abnormalities." PT/INR is a measurement of blood clotting, and is used to monitor the effectiveness of anticoagulant therapies.

To find information on coumarins, the researchers searched the NAPRALERT (Natural Products ALERT) database. Out of a known 3400 natural coumarins occurring in 160 plant families, only 13 "have been evaluated for antithrombotic or anticoagulant activity." And of those, only seven were active. Coumarins are a class of plant compounds that possess many different chemical structures. Coumarins were initially isolated from the tonka bean (*Dipteryx odorata*) in the 1800s.

Research still needs to determine if isolated individual coumarins have any effects on coagulation and whether or not the concentration of coumarins present in a plant or dietary

supplement poses any danger. The authors pose several questions: (1) How much anticoagulant coumarins are present in a product? (2) What dose of coumarins will be ingested with the supplement? (3) How much of the coumarin will actually be absorbed by the intestines once ingested? (4) What dose would be required to cause anticoagulant effects? and (5) Has the effect been established in clinical trials?

A lack of good evidence and understanding of the research can lead to misunderstanding. For example, dicoumarol, a coumarin found in moldy hay made from *Melilotus alba* or *Melilotus officinalis* was responsible for the hemorrhagic death of livestock in 1941. *Melilotus* spp. are commonly referred to as "sweet clover." *Trifolium pratense* is also sometimes called sweet clover, but the actual common name is red clover. "Because of this unfortunate redundancy...some researchers and clinicians have been led to believe that red clover is a potential source of dicoumarol, and therefore consumption of red clover dietary supplements presents a risk to patients taking warfarin or other anticoagulants," they write. This concern is also reported "regularly" in the literature. However, the occurrence of dicoumarol in *T. pratense* has not been substantiated.

The authors of this research conducted a clinical trial to determine if coumarins with known anticoagulant effects occur in *T. pratense*, if they occur in sufficient concentrations to potentially alter PT/INR, and whether or not *T. pratense* alters PT/INR in volunteers. Seventeen coumarins were purchased from Indofine (Somerville, NJ), Sigma (St Louis, MO) or TimTec (Newark, DE). None of the 17 coumarins were detected in a red clover extract (PureWorld Botanicals, South Kachensack, NJ) at concentrations greater than 0.3% dry weight. This means that "consumption of 400 mg/day of this red clover extract would result in a dose of less than 0.28 mg/day (690 ppm) of all 17 coumarins combined." Dicoumarol doses of 25–200 mg/day are needed to produce clinically significant anticoagulant effects, and the concentration of dicoumarol in the extract was about 100 times less than the lowest dose. To consume 25 mg/day of dicoumarol, a person would have to ingest 250 grams of red clover extract per day. Red clover extract given to volunteers to relieve hot flashes was given at a dose of 400 mg/day, and the PT/INR was not changed in any of the 25 volunteers taking this extract for one month.

Much research remains to be conducted, but this study provides a rational framework for evaluating and considering the health implications of natural coumarins. The safety profile for the red clover extract analyzed in this article seems excellent, but these conclusions may not be applicable to other red clover extracts. Since so many people are taking dietary supplements, clinicians should strive to educate themselves in how natural products may benefit or harm their patients.

—John Neustadt, ND

Enclosure: Referenced article reprinted with permission from Elsevier, Inc.

The American Botanical Council provides this review as an educational service. By providing this service, ABC does not warrant that the data is accurate and correct, nor does distribution of the article constitute any endorsement of the information contained or of the views of the authors.

ABC does not authorize the copying or use of the original articles. Reproduction of the reviews is allowed on a limited basis for students, colleagues, employees and/or members. Other uses and distribution require prior approval from ABC.