QUERCETIN

A MEDICAL DICTIONARY, BIBLIOGRAPHY,
AND ANNOTATED RESEARCH GUIDE TO
INTERNET REFERENCES

JAMES N. PARKER, M.D.
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The collective knowledge generated from academic and applied research summarized in various references has been critical in the creation of this book which is best viewed as a comprehensive compilation and collection of information prepared by various official agencies which produce publications on quercetin. Books in this series draw from various agencies and institutions associated with the United States Department of Health and Human Services, and in particular, the Office of the Secretary of Health and Human Services (OS), the Administration for Children and Families (ACF), the Administration on Aging (AOA), the Agency for Healthcare Research and Quality (AHRQ), the Agency for Toxic Substances and Disease Registry (ATSDR), the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), the Healthcare Financing Administration (HCFA), the Health Resources and Services Administration (HRSA), the Indian Health Service (IHS), the institutions of the National Institutes of Health (NIH), the Program Support Center (PSC), and the Substance Abuse and Mental Health Services Administration (SAMHSA). In addition to these sources, information gathered from the National Library of Medicine, the United States Patent Office, the European Union, and their related organizations has been invaluable in the creation of this book. Some of the work represented was financially supported by the Research and Development Committee at INSEAD. This support is gratefully acknowledged. Finally, special thanks are owed to Tiffany Freeman for her excellent editorial support.

About the Editors

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FORWARD

In March 2001, the National Institutes of Health issued the following warning: "The number of Web sites offering health-related resources grows every day. Many sites provide valuable information, while others may have information that is unreliable or misleading."[1] Furthermore, because of the rapid increase in Internet-based information, many hours can be wasted searching, selecting, and printing. Since only the smallest fraction of information dealing with quercetin is indexed in search engines, such as **www.google.com** or others, a non-systematic approach to Internet research can be not only time consuming, but also incomplete. This book was created for medical professionals, students, and members of the general public who want to know as much as possible about quercetin, using the most advanced research tools available and spending the least amount of time doing so.

In addition to offering a structured and comprehensive bibliography, the pages that follow will tell you where and how to find reliable information covering virtually all topics related to quercetin, from the essentials to the most advanced areas of research. Public, academic, government, and peer-reviewed research studies are emphasized. Various abstracts are reproduced to give you some of the latest official information available to date on quercetin. Abundant guidance is given on how to obtain free-of-charge primary research results via the Internet. **While this book focuses on the field of medicine, when some sources provide access to non-medical information relating to quercetin, these are noted in the text.**

E-book and electronic versions of this book are fully interactive with each of the Internet sites mentioned (clicking on a hyperlink automatically opens your browser to the site indicated). If you are using the hard copy version of this book, you can access a cited Web site by typing the provided Web address directly into your Internet browser. You may find it useful to refer to synonyms or related terms when accessing these Internet databases. **NOTE:** At the time of publication, the Web addresses were functional. However, some links may fail due to URL address changes, which is a common occurrence on the Internet.

For readers unfamiliar with the Internet, detailed instructions are offered on how to access electronic resources. For readers unfamiliar with medical terminology, a comprehensive glossary is provided. For readers without access to Internet resources, a directory of medical libraries, that have or can locate references cited here, is given. We hope these resources will prove useful to the widest possible audience seeking information on quercetin.

The Editors

[1] From the NIH, National Cancer Institute (NCI): **http://www.cancer.gov/cancerinfo/ten-things-to-know**.

CHAPTER 1. STUDIES ON QUERCETIN

Overview

In this chapter, we will show you how to locate peer-reviewed references and studies on quercetin.

The Combined Health Information Database

The Combined Health Information Database summarizes studies across numerous federal agencies. To limit your investigation to research studies and quercetin, you will need to use the advanced search options. First, go to **http://chid.nih.gov/index.html**. From there, select the "Detailed Search" option (or go directly to that page with the following hyperlink: **http://chid.nih.gov/detail/detail.html**). The trick in extracting studies is found in the drop boxes at the bottom of the search page where "You may refine your search by." Select the dates and language you prefer, and the format option "Journal Article." At the top of the search form, select the number of records you would like to see (we recommend 100) and check the box to display "whole records." We recommend that you type "quercetin" (or synonyms) into the "For these words:" box. Consider using the option "anywhere in record" to make your search as broad as possible. If you want to limit the search to only a particular field, such as the title of the journal, then select this option in the "Search in these fields" drop box. The following is what you can expect from this type of search:

- **Quercetin in Men with Category III Chronic Prostatitis: A Preliminary Prospective, Double-Blind, Placebo-Controlled Trial**

  Source: Urology. 54(6): 960-963. December 1999.

  Contact: Available from Urology. P.O. Box 2126, Marion, OH 43306-8226. (800) 215-4692. Fax (740) 382-5866.

  Summary: The National Institutes of Health (NIH) category III chronic prostatitis syndromes (nonbacterial chronic prostatitis and prostatodynia or prostate pain) are common disorders with few effective therapies. Bioflavonoids have recently been shown in an open-label study to improve the symptoms of these disorders in a significant proportion of men. This article reports on a study undertaken to confirm these findings in a prospective randomized, double-blind, placebo controlled trial. The study included

30 men with category IIIa and IIIb chronic pelvic pain syndrome who were randomized in a double blind fashion to receive either placebo or the bioflavonoid **quercetin** 500 milligrams twice daily for 1 month. The NIH chronic prostatitis symptom score was used to grade symptoms and the quality of life impact at the start and conclusion of the study. In a followup, unblind, open label study, 17 additional men received 1 month of a supplement containing **quercetin,** as well as bromelain and papain (Prosta-Q), which enhance bioflavonoid absorption. Two patients in the placebo group refused to complete the study because of worsening symptoms, leaving 13 placebo and 15 bioflavonoid patients for evaluation in the blind study. Both the **quercetin** and placebo groups were similar in age, symptom duration, and initial symptom score. Patients taking placebo had a mean improvement in NIH symptom score from 20.2 to 18.8 (not significant), while those taking the bioflavonoid had a mean improvement from 21.0 to 13.1. Twenty percent of patients taking placebo and 67 percent of patients taking the bioflavonoid had an improvement of symptoms of at least 25 percent. In the 17 patients who received Prosta-Q in the open label study, 82 percent had at least a 25 percent improvement in symptom score. The authors conclude that therapy with the bioflavonoid **quercetin** is well tolerated and provides significant symptomatic improvement in most men with chronic pelvic pain syndrome. 1 figure. 1 table. 26 references.

Federally Funded Research on Quercetin

The U.S. Government supports a variety of research studies relating to quercetin. These studies are tracked by the Office of Extramural Research at the National Institutes of Health.[2] CRISP (Computerized Retrieval of Information on Scientific Projects) is a searchable database of federally funded biomedical research projects conducted at universities, hospitals, and other institutions.

Search the CRISP Web site at **http://crisp.cit.nih.gov/crisp/crisp_query.generate_screen**. You will have the option to perform targeted searches by various criteria, including geography, date, and topics related to quercetin.

For most of the studies, the agencies reporting into CRISP provide summaries or abstracts. As opposed to clinical trial research using patients, many federally funded studies use animals or simulated models to explore quercetin. The following is typical of the type of information found when searching the CRISP database for quercetin:

- **Project Title: ALCOHOL POLYPHENOL INDUCED ENDOTHELIAL FIBRINOLYSIS**

  Principal Investigator & Institution: Booyse, Francois M.; Professor of Medicine & Cell Biol.; University of Alabama at Birmingham Uab Station Birmingham, Al 35294

  Timing: Fiscal Year 2003; Project Start 01-JUL-2003; Project End 30-JUN-2008

  Summary: Moderate alcohol or red wine consumption (1-4 drinks/day) reduces the risk for CHD-related mortality. This cardioprotection may be due, in part, to increased fibrinolysis. Endothelial cells (ECs) synthesize t-PA, u-PA, PAI-1 and receptors (Rs) for

[2] Healthcare projects are funded by the National Institutes of Health (NIH), Substance Abuse and Mental Health Services (SAMHSA), Health Resources and Services Administration (HRSA), Food and Drug Administration (FDA), Centers for Disease Control and Prevention (CDCP), Agency for Healthcare Research and Quality (AHRQ), and Office of Assistant Secretary of Health (OASH).

PAs and plasminogen (Pmg) (PARs, PmgRs) and maintain normal hemostasis/fibrinolysis by activating R-bound Pmg through the regulated synthesis/interactions of these fibrinolytic components. Changes in these EC components/interactions by systemic factors (such alcohol, wine components, in particular polyphenols) that increase fibrinolysis will reduce the risk for thrombosis, atherosclerosis/CHD and the atherothrombotic consequences of MI. We have shown that ethanol/polyphenols increase fibrinolysis in cultured human ECs. The overall goal of these studies is to further identify/define the molecular regulatory mechanisms by which low ethanol/polyphenols (catechin, quercetin) affect the activity/expression of EC PAs, PARs and PmgRs, in vitro and in vivo, resulting in increased EC fibrinolysis. Studies will include effects on: expression of PAs/PARs/PmgRs antigen/mRNA in vivo in mouse aortic endothelium, including direct effects of increased fibrinolysis, in vivo, on clot lysis and inhibition of atherosclerosis in wild type and genetically deficient mice (Aim 1); in vivo and in vitro cross-talk between induced increased fibrinolysis and increased bioavailability of NO, including early activation of cellular kinases (i.e. MAPKs) (Aim 2); changes in expression of EC PARs/PmgRs activity/levels/mRNA (in cultured human coronary artery ECs), including individual R contribution to total ligand binding (using R-specific antisense oligonucleotides), regulation of Rs gene expression (transcriptional and/or post-transcriptional) and other PA-induced effects on PARs/PmgRs expression (in cultured PA-deficient mouse aortic EC) (Aim 3) and; identification of ethanol/polyphenol responsive cis-acting elements in the t-PA and u-PA gene promoters, including their ethanol-/polyphenol-inducible transcription factors (Aim 4). Results gleaned from these studies will provide new insights into the molecular mechanisms by which ethanol/polyphenols regulate EC fibrinolysis and contribute to the cardioprotection attributed to moderate alcohol/red wine consumption. An increased understanding of the mechanisms by which these compounds effectively afford cardioprotection will facilitate future development of new therapeutic approaches/strategies that may be widely applied to reduce the overall population risk for CHD-related mortality.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: BORAGE OIL AND GINKGO BILOBA (EGB 761) IN ASTHMA**

  Principal Investigator & Institution: Gershwin, Merrill E.; Internal Medicine; University of California Davis Sponsored Programs, 118 Everson Hall Davis, Ca 95616

  Timing: Fiscal Year 2002; Project Start 18-SEP-2000; Project End 31-JUL-2005

  Summary: Project I: Borage Oil and Ginkbo biloba (EGb 761) in Asthma, ME Gershwin, PI overall; V Ziboh, PI of Oil, Co-Invest; SS Teuber, PI of Ginkbo biloba; M Harkey, JB German & c Cross, Co-Invest; J Utts, M Watnik, AL Klassen, Statistics and Database Management; H Watanabe, Consultant The concept of asthma as a condition in which acute and chronic inflammatory changes in airways play a fundamental role is well established. The role of leukotrienes as a crucial element of these inflammatory processes is supported by abundant laboratory and clinical evidence. There is a potential for herbal medicinal approaches to ameliorate leukotriene-mediated inflammation in asthma based on data from the literature and our laboratory. Studies suggest that dietary gamma-linolenic (GLA), found in borage and evening primrose oil, is unique among the (n=6) polyunsaturated fatty acid family members (linolenic acid, GLA and arachidonic acid) in its potential to attenuate inflammatory processes. For instance, there are randomized, placebo- controlled trials (RCT) demonstrating efficacy of dietary GLA in patients with rheumatoid arthritis and active synovitis. Ginkbo biloba, a flavonoid-rich extract of leaves of the Ginkbo biloba tree, has been studied in one RCT

with asthma patients and is recommended by CAM practitioners as a treatment of allergic inflammation and asthma. Ginko biloba may have inhibitory effects on release of inflammatory mediators. Although improvements has been made in management of patients with asthma, may interventions are associated with adverse effects. Because of the possibility of minimal or negligible adverse effects reported with borage oil, and the widespread use of Ginkgo biloba supplements without known adverse effects, we will assess clinical efficacies and/or adverse effects of dietary borage oil containing GLA and Ginkbo biloba in patients with asthma in a 17 month RCT. We also propose to delineate whether or not the clinical course of treatment correlates with suppression of leukotriene B4 (LTB4), LTC4 and LTD4, generated by activated polymorphonuclear cells (PMNs). Additionally, in the Ginkgo biloba arm of study, the vitro/ex vivo inhibition of histamine release will be assayed, since one of its major constituents, **quercetin,** is known to be structurally related to cromolyn sodium and has been shown in in vitro studies to exhibit similar activities. Furthermore. Anti-inflammatory activities of Ginkbo biloba will be compared to those of some of its individual constituents in a series of in vitro experiments. It is hoped that findings from these studies will evolve relatively non-toxic therapeutic alternatives for attenuating bronchial hyperresponsiveness and inflammation in patients with asthma.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: CARDIOVASCULAR EFFECTS OF SCUTELLARIA BAICELENSIS**

  Principal Investigator & Institution: Yuan, Chun-Su; Anesthesia and Critical Care; University of Chicago 5801 S Ellis Ave Chicago, Il 60637

  Timing: Fiscal Year 2002; Project Start 20-SEP-2001; Project End 31-AUG-2003

  Summary: (provided by applicant): Cardiovascular disease remains a leading cause of death throughout the world, with many dying outside the hospital due to cardiac arrest. Although oxidants may play an important role in this major cardiovascular disease, little has been done to examine what role traditional vs. nontraditional antioxidants may play in its acute treatment. During the past year, our group investigated cardioprotective effects of Scutellaria baicalensis, a Chinese medicinal herb. We reported that an extract of Scutellaria baicalensis dose-dependently attenuated reactive oxygen species in cardiomyocytes and decreased cell death. We were particularly excited to observe that Scutellaria baicalensis extract rapidly quenched reactive oxygen species generated in mitochondria. The ability to gain rapid access to intracellular sites, such as mitochondria, and attenuate reactive oxygen species is a significant advantage, a characteristic that may be lacking in antioxidants currently in use. In separate studies, we observed that **quercetin,** a plant flavonoid, inhibited endothelin-1 and stimulated tissue plasminogen activator in vascular endothelial cells. Thus, we hypothesize that flavonoids of Scutellaria baicalensis have significant antioxidant potential, and they regulate the concentration of endothelial vasoactive mediators. Heart disease is a complex multifactorial disorder with a variety of underlying causes and risk factors. In the development of ischemic heart disease, the site of initial injury is the vascular endothelium. During later stages, ischemic and reperfusion injury to cardiomyocytes lead to loss of contractility and cell death. We propose to investigate in vitro pharmacological effects of Scutellaria baicalensis in two experimental models: embryonic chick cardiomyocytes, and human umbilical vein endothelial cells. In the proposed project, we will identify active flavonoids of Scutellaria baicalensis and investigate their 1) antioxidant action in cardiomyocytes, and 2) pharmacological effects on vasoactive mediators in endothelial cells. We will test whether Scutellaria baicalensis extract and its flavonoids (baicalein and wogonin, skullcapflavone I, and

skullcapflavone II) act as antioxidants in cardiomyocytes, and test whether Scutellaria baicalensis extract and its flavonoids change the concentration of thrombin-stimulated endothelin-1, and tissue plasminogen activator in vascular endothelial cells. In addition, antioxidant activity comparison will be made between Scutellaria baicalensis and American ginseng. The results of our project will be used to develop potential new therapeutic agents from active components of Scutellaria baicalensis.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: CHEMICO-PHYSICAL PROPERTIES OF METAL-FLAVONOID**

  Principal Investigator & Institution: Cheng, Francis I.; Chemistry; University of Idaho Moscow, Id 838443020

  Timing: Fiscal Year 2001; Project Start 01-APR-2001; Project End 31-MAR-2005

  Summary: (provided by applicant) Flavonoids are recognized as an important class of nutrient that may be responsible for the chemoprevention of a myriad of degenerative diseases. This action is attributed to their putative antioxidant action. Many investigators have recognized that metal chelation is an important determinate in the prediction of the antioxidant action of flavonoids. However, there is a paucity of data accumulated concerning the chemico-physico properties of metal-flavonoid complexes. A previous investigation from this laboratory has found that four flavonoids, baicilein, luteolin, naringenin, and **quercetin,** chelate pro-oxidant iron ions into a complex that is not Fenton Reaction active. Another plant-borne product, salicylate has been the subject of previous investigations from this laboratory and found to chelate pro-oxidant iron into a form that is again not Fenton Reaction active. The proposed investigations will study the similarity of action between the four aforementioned flavonoids and salicylate, i.e. the ability to bind pro-oxidant metals both as free ions and in low molecular-weight complexes. The pro-oxidant metals of concern in this study are Fe, Cu, and Mn ions and also in complexed forms with EDTA, ATP/ADP and in porphyrins. The redox potential of each metal complex will predict the antioxidant characteristics in terms of Fenton Reaction activity, other redox-dependent actions such as superoxide dismutase and catalase activity. Metal-flavonoid binding constants will aid in determining if the flavonoids are effective in vivo chelation agents. These data will be derived by potentiometric titrations augmented with UV-vis absorbance. The four flavonoids chosen for this study will give insights into structure-activity relationships. It is hoped that the subject of this investigation will give a new paradigm for the design, and discovery of antioxidants, and anti-inflammatory agents.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: DRUG INTERACTIONS AND BIOAVAILABILITY OF CRANBERRY**

  Principal Investigator & Institution: Donovan, Jennifer L.; Psychiatry and Behavioral Scis; Medical University of South Carolina 171 Ashley Ave Charleston, Sc 29425

  Timing: Fiscal Year 2004; Project Start 06-JAN-2004; Project End 31-DEC-2005

  Summary: (provided by applicant): Cranberry (CB) juice and powders are currently being used as complementary and alternative medications. CB products may be used alone or in combination with conventional medications to treat urinary tract infection, or other medications to treat acute or chronic conditions. CB is a rich source of flavonoids, a class of phytochemicals with diverse biological activities. The specific aims of this research are 1) to evaluate the potential for CB-drug interactions and 2) to determine the pharmacokinetics and renal clearance of four major CB flavonoids. A normal volunteer study is proposed to determine the potential of CB to participate in interactions with

conventional drugs. The induction/inhibition of the major cytochrome P-450 (CYP) enzymes will be the primary method of evaluation. The CYP isoforms to be studied, CYP3A4, CYP2D6 and CYP1A2, are involved in the metabolism of >80% of marketed prescription and over the counter medications. Single doses of the three safe, probe drugs alprazolam (ALPZ; 3A4 probe), dextromethorphan (DM; CYP2D6 probe), and caffeine (CAF; CYP1A2 probe) will be administered at baseline (before treatment with CB) and after a 14-day treatment period with CB powder. Changes in the pharmacokinetics of these probe drugs will indicate the degree of specific enzyme inhibition or induction. In the same normal volunteers, the key pharmacokinetic parameters for four major CB flavonoids will be estimated by following the plasma concentration versus time course of absorbed flavonoids and their excretion in urine. The area under the plasma concentration versus time curve (AUC), oral clearance (Clo), terminal elimination half-life (T1/2) and renal clearance (Clren) will be determined for: epicatechin, **quercetin** (total glycosides), procyanidin A2, and cyanidin-3-galactoside. These components represent the major classes of flavonoids in CB and are selected for study due to their abundance in CB and their documented biological activities. The pharmacokinetics and renal clearance of CB flavonoids will be determined first after a single dose of a characterized CB juice prior to administration of any probe drugs. Steady-state plasma levels of flavonoids will be determined at the end of the 14-day treatment period of multiple dosing with the characterized CB powder. This research will provide new, important data on the pharmacokinetics of flavonoids from CB juice and from a CB powder, an area where no data currently exist. This information is essential to elucidate the mechanisms of action of CB flavonoids in the context of specific conditions/diseases and to evaluate CB as a source of dietary flavonoids. These data will also complement NCCAM studies assessing the clinical safety and efficacy of CB and will allow more informed recommendations about the use of CB when combined with conventional medications.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: DRUG-DIETARY FLAVONOID INTESTINAL ABSORPTION INTERACTION**

  Principal Investigator & Institution: Rodriguez, Rosita J.; None; Oregon State University Corvallis, or 973391086

  Timing: Fiscal Year 2002; Project Start 17-SEP-2001; Project End 31-AUG-2004

  Summary: (provided by applicant): The opportunity for drug-dietary interaction is an everyday occurrence whether the interaction is with food, juice, or dietary supplements. Moreover, the consumption of flavonoids is being urged because of their multiple health benefits; thus, understanding the possible biological effects of the flavonoids on intestinal drug absorption is essential. Flavonoids may be a particularly important class of modulators due to their ubiquitous occurrence in foods and drinks of plant origin and their known interactions with P-glycoprotein (Pgp) and cytochrome P450 (CYP). These dietary constituents may modulate transport in the intestinal tract and significantly alter the absorption of important therapeutic agents. The increased systemic bioavailability of some drugs, nifedipine and felodipine, associated with ingestion of grapefruit juice represents a couple of widely publicized drug-dietary-interactions. An increase or decrease in drug absorption may be due to (i) alterations in Pgp mediated or non Pgp mediated transport and/or (ii) presystemic intestinal metabolism by CYP and/or the flavin-containing monooxygenases. Furthermore, patents have been filed which incorporate flavonoids as excipients in pharmaceutical formations with the intent to alter drug absorption. Thus, the specific hypothesis of this study is that dietary

flavonoids can alter the Pgp-dependent or Pgp-independent transport of certain therapeutic drugs. Studies will be conducted using flavonoids belonging to different subclasses such as isoflavone, flavanone, flavonol, and flavanol (e.g., genistein, naringenin, **quercetin,** and epigallocatechin gallate, respectively) to gain an insight into structure-activity relationships in the alteration of transport of Pgp-dependent substrates and Pgp-independent substrates by these phytochemicals. The flavonoids will be evaluated using Caco-2 cells, a human intestinal cell line. These cells have been well characterized to express Pgp transporters and non Pgp transporters such as Na+/K+, Na+/H+, amino acids, peptides, bile acid, and vitamin B12. This project will provide new knowledge on how flavonoids affect the dynamic transport mechanisms located in the intestinal mucosa. Thus, the results of this study will increase our understanding of the role of flavonoids found in tea, vegetables, soy, and dietary supplements in the intestinal absorption of therapeutic drugs.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: EFFECT OF PLANT PHENOLIC COMPOUNDS ON HUMAN COLON EPITHELIAL CELLS**

  Principal Investigator & Institution: Shiff, Steven J.; Associate Professor of Clinical Investig; Rockefeller University New York, Ny 100216399

  Timing: Fiscal Year 2002

  Summary: Colorectal cancer is a common and often fatal cancer. Primary prevention of this important public health problem is feasible because it is substantially influenced by nutritional and pharmacological factors such as dietary fat, fiber, micronutrients (i.e. calcium and selenium, aspirin (ASA), and other nonsteroidal antiinflammatory drugs. Sulindac is a potent chemopreventive agent for colorectal cancer. **Quercetin,** a plant-derived compound with anti-inflammatory properties, inhibits colon cancer development in preclinical studies. However, its effectiveness in the prevention of human colorectal cancer is unknown. NSAIDs modulate the turnover (induce cell quiescence and apoptosis) of colonic epithelial cells. This effect may be important for their efficacy as colon cancer chemopreventive agents. The goal of this study is to determine the effects sulindac and **quercetin** on the turnover of human colonic epithelial cells. By comparing and contrasting the effect of these 2 compounds on colonocytes of humans, we hope to begin to understand the effects of NSAID compounds on the physiology of the colorectal crypts of humans. Through these and future studies we eventually hope to predict the potential utility of **quercetin** as a colon cancer chemopreventive agent and to shed additional light on the mechanisms by which anti-inflammatory agents prevent colon carcinogenesis.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: FLAVONOID BIOAVAILABILITY IN HUMANS-CELLULAR STUDIES**

  Principal Investigator & Institution: Walle, Thomas; Professor; Pharmacology; Medical University of South Carolina 171 Ashley Ave Charleston, Sc 29425

  Timing: Fiscal Year 2002; Project Start 01-FEB-1998; Project End 31-JUL-2006

  Summary: (provided by applicant): The long-term goal of this research program is to increase our understanding of how cellular transport and metabolism influence the oral bioavailability of dietary flavonoids, a large class of compounds that has been implicated to play a major role in the prevention of human diseases, in particular cardiovascular disease and cancer. In Specific Aim 1 we will determine the

interrelationships between SGLT1 and MRP2, including mechanisms involved, in the enterocyte absorption of flavonoid glycosides and the tea flavonoids, two main classes of dietary flavonoids. These studies will be undertaken in SGLT1- and MRP2-transfected cells and in the human intestinal absorption model Caco-2. The role of the potentially most important transporter, i.e. MRP2, will be directly examined in vivo in the MRP2-deficient Tr- rat. In Specific Aim 2 we will investigate the interrelationships between CYPs, UGTs and SULTs, including the identification of the major isoforms involved, in the hepatic as well as intestinal metabolism of flavonoids. This will be done in microsomes as well as in intact cells, e.g. fresh human hepatocytes. These experiments will allow us to establish the major pathway(s) of metabolism of the flavonoids. In addition, autoinduction of flavonoid metabolism will be examined, mainly focusing on CYPs and UGTs. The importance of the UGT family of enzymes will be directly examined in vivo in the genetically deficient Gunn rat. In Specific Aim 3 we will determine the role and mechanisms of a) bacterial- and b) peroxidase-mediated catabolism of flavonoids, including covalent binding to protein. The experiments in a) will be conducted in gnotobiotic compared to normal rats as well as in samples from an in vivo human study. Complementary in vitro studies will include the identification of the bacterial pathway leading from **quercetin** to CO2 formation. The experiments in b) will be conducted in vitro, using pure enzymes and subcellular fractions, and then in intact cell systems in which production of reactive oxygen species as well as glutathione levels can be manipulated. Structure identification of metabolites as well as elucidation of covalent binding will be critical factors. The findings from the proposed studies should help us understand the bioavailability of the flavonoids, facilitating optimization of the chemopreventive utility of these natural or synthetic compounds.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: HEAT SHOCK PROTEINS AND DRUG RESISTANCE**

  Principal Investigator & Institution: Fuqua, Suzanne A.; Professor; University of Texas Hlth Sci Ctr San Ant 7703 Floyd Curl Dr San Antonio, Tx 78229

  Timing: Fiscal Year 2002

  Summary: Heat shock proteins (hsp's) protect cells from a variety of stresses. Human breast cancer cells may express high levels of hsp27 and hsp70 in particular, which we have found to be associated with general tumor aggressiveness. Preliminary evidence also suggests that hsp's play a role in drug resistance, and understanding the mechanisms involved could lead to clinical strategies to circumvent such resistance and improve patient survival. We initially found that heat shock increases the resistance of breast cancer cells to doxorubicin, while inducing hsp27 and hsp70. Introducing hsp27 cDNA makes the cells resistant to doxorubicin, while blocking hsp27 expression with flavones (e.g. quercitin) reverses resistance. We now need to determine whether hsp70 plays a similar role. We also plan to further investigate means of modulating hsp27 expression for therapeutic benefit by manipulating its regulatory promoter system - we have already identified key elements of the promoter region to be targeted, along with a novel DNA-binding protein which binds one of these elements. We will examine mechanisms which may be involved in the association of hsp's with drug resistance, and confirm the association in clinical breast cancer specimens from doxorubicin-resistant vs. naive patients. Our Specific Aims are: (1) To confirm our preliminary finding that hsp70 may also play a role in doxorubicin resistance in human breast cancer cells. We will use antisense oligonucleotides to inhibit expression of both hsp70 and its constitutive cognate hsc70 in breast cancer cells, and full-length cDNAs to induce overexpression, determining drug resistance in soft agar cloning assays and in vivo

nude mouse studies. (2) To further develop pharmacologic means (flavone inhibition) and molecular means (promoter studies) to circumvent hsp27-induced doxorubicin resistance. (3) To search for mechanisms associated with this resistance, focusing in particular on the role of topoisomerase II. (4) To translate these findings to the clinical setting by determining the relationship of hsp27 and hsp70 with clinical doxorubicin resistance. We will compare hsp levels in a set of 100 doxorubicin-resistant metastases vs. 100 naive breast cancer specimens, and will also correlate hsp levels with clinical outcome in a prospective, randomized adjuvant clinical trial (SWOG 8897) involving doxorubicin. All of this will prepare for a Phase I clinical trial directed at circumventing hsp-induced doxorubicin resistance using the pharmacologic agent quercitin, though the trial itself is not a part of the present proposal, and will also suggest other approaches for reversing resistance to this otherwise most useful drug in breast cancer treatment.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: IMMUNOBIOLOGY OF WALNUT FOOD ALLERGY**

  Principal Investigator & Institution: Teuber, Suzanne S.; Internal Medicine; University of California Davis Sponsored Programs, 118 Everson Hall Davis, Ca 95616

  Timing: Fiscal Year 2002; Project Start 01-MAY-1999; Project End 30-APR-2003

  Summary: Over the last ten years, genes encoding food allergens have been cloned and sequenced but no consensus sequences or motifs associated with allergy have been determined. Indeed, my lab has cloned genes encoding 2 of the major English walnut kernel allergens, the 2S albumin and a vicilin-like seed storage protein, Jug r 1 and Jug r 2, respectively. Plant seed allergy is often life-threatening and permanent. Individuals with walnut allergy, for instance, can have high levels of specific IgE against several different, non-cross-reactive proteins in their sera into their seventh decade. Most patients who have life-threatening walnut allergy have a childhood history of atopic dermatitis (AD), in which it has been demonstrated that there is more of a tendency to develop IgE against multiple environmental and food allergens. Even in the face of this however, most children with AD are tolerant of most foods. The major thesis of this proposal is that plant seed proteins, because of the way they are packaged as whole proteins in the plant protein body storage organelle with associated lectins, enzymes, and polyphenolic compounds, are able to stimulate the APC in atopic persons to modulate the cytokine milieu towards increased IL-4 and IL-13, inducing an IgE response. As a prototype seed to study, the walnut (Juglans regia) will be used based on the availability of human subjects, recombinant allergens, multiple protein preparations, fractionated polyphenolics and its importance as a tree nut allergen. To characterize the APC-T cell interaction, T cell lines will be established from individuals with walnut food allergy and individuals with atopic dermatitis without food allergy. The proliferative response and Th2 related cytokine mRNA transcription will be assessed in response to different antigen packages delivered to the APC: recombinant Jug r 1 and Jug r 2, peptide fragments, whole purified proteins (albumins and large globulins), purified protein bodies (lectins and enzymes present), total walnut extract (pellicle polyphenolics and oil body lipids present), and the above protein sources with a quantified walnut total polyphenolic fraction added (rich in **quercetin** and ellagic acid). The above data will significantly advance our knowledge of the immunobiology of plant seed allergy.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: INFLUENCE OF CRANBERRY ON PLAQUE-RELATED DISEASES**

  Principal Investigator & Institution: Koo, Hyun; Eastman Dentistry; University of Rochester Orpa - Rc Box 270140 Rochester, Ny 14627

  Timing: Fiscal Year 2004; Project Start 01-JAN-2004; Project End 30-NOV-2006

  Summary: (provided by applicant): Dental caries is the most common oral infectious disease that afflicts humans. More than 95% of all adults have experienced this disease. It is more common than asthma, hay fever or chronic bronchitis in 5-17 year old children. The American public spends close to $40 billion per year to treat this disease or its consequences. Dental caries results from the interaction of specific bacteria with constituents of the diet on a susceptible tooth surface. Dental plaque accumulation is the first clinical evidence of this interaction; dental plaque is a biofilm which is comprised of a population of bacteria growing on the tooth surface enmeshed in a polysaccharide matrix. Acid can be formed rapidly by acidogenic bacteria, such as Streptococcus mutans, within the matrix and its persistence results in dissolution of the tooth. Furthermore, plaque is also the major aetiological factor in gingivitis. Cranberries, like other natural products, harbor a plethora of biological compounds such as flavonoids (e.g. **quercetin** and myricetin), phenolic acids (benzoic acid), anthocyanins, condensed tannins, and others. We have shown that many of these substances can: (i) inhibit enzymes associated with the formation of the plaque polysaccharide matrix, (ii) block adherence of bacteria to surfaces, (iii) prevent acid formation, and (iv) reduce acid tolerance of cariogenic organisms. For example, **quercetin** and myricetin are effective inhibitors of glucosyltransferases (GTFs), enzymes responsible for the synthesis of glucans; glucans synthesized by GTFs mediate the adherence and accumulation of cariogenic streptococci on the tooth surface. Weak acids, such as benzoate (benzoic acid), affect the acid production by S. mutans and have been shown to reduce dental caries in rats. We propose a comprehensive plan to explore the influence of cranberry on many of the biological aspects involved in the pathogenesis of dental plaque formation and caries. We also propose to examine the ability of cranberry to prevent or reduce caries in our well-proven rodent model and to investigate the effects of cranberry on plaque formation and gingivitis in vivo.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: INFLUENCE OF DIETARY FLAVONOIDS ON THE EXPRESSION OF AT***

  Principal Investigator & Institution: Keen, Carl L.; Professor and Chairman; Nutrition; University of California Davis Sponsored Programs, 118 Everson Hall Davis, Ca 95616

  Timing: Fiscal Year 2002; Project Start 15-SEP-2001; Project End 31-AUG-2004

  Summary: (provided by applicant) Oxidative stress is characterized by excessive concentrations of reactive oxygen and reactive nitrogen species (ROS and RNS). Excessive oxidative damage has been implicated in the pathogenesis of numerous degenerative diseases including coronary vascular diseases (CVD). A current hypothesis suggests that ROS, RNS and oxidized LDL (ox-LDL) induce the expression of atherogenic genes via redox-sensitive signaling pathways. The oxidative stress-induced gene expression has been shown to be mediated via the activation of redox sensitive transcription factors such as nuclear factor- kappaBeta (NFkB), and redox-sensitive transduction pathways such as those involving members of the mitogen activated protein kinase (MAPK) family as well as members of the Src family. Genes regulated by NFkB activation encode for proteins implicated in acute phase and inflammatory responses including certain cytokines and chemokines, cell adhesion molecules and