

PRINCIPAL INVESTIGATOR:

APPLICATION:

REVIEWER:

ORGANIZATION:

SAMPLE

OVERALL EVALUATION: This is the first submission of a new application from a junior investigator to conduct a limited clinical trial to test the hypothesis that purple grape juice may function as an alternative pharmacotherapeutic agent to aspirin to serve as an inhibitor of platelet aggregation and thus serve as treatment or preventative of cardiovascular and cerebrovascular disease. The proposal is well written, contains a testable hypothesis and possesses many strengths and few weaknesses. The application is likely to generate significant new and useful information suitable for support of future extramural applications and the proposal generates very substantial enthusiasm.

SCORE:

DESCRIPTION: Aspirin is widely utilized for the treatment and prevention of cardiovascular and cerebrovascular disease. Limitations of aspirin therapy for these disease states is limited by adverse effects and substantial inter individual responsiveness to this drug. Alternative therapies are expensive, of unproven clinical effectiveness or both. This application will test the efficacy of purple grapefruit juice to serve as a clinically effective alternative inhibitor of platelet aggregation for antithrombotic effects. A secondary goal will be to investigate potential therapeutic effects of purple grapefruit juice on serum cholesterol and homocysteine levels. Healthy volunteers will be tested in the UNM General Clinical Research Center for the in vivo effects of purple grapefruit juice on platelet aggregation, serum cholesterol and homocysteine levels in order to obtain preliminary data to support applications for funding for larger clinical trials.

CRITIQUE:

1) SIGNIFICANCE: This application addresses a timely and important question directly relevant to human health. Aspirin is a widely utilized drug for the prevention and treatment of cardiovascular and cerebrovascular disease, both of which are significant human health problems. Unfortunately, the utility of this widely utilized pharmacotherapeutic protocol is significantly limited due to adverse side effects (primarily gastrointestinal) and the wide inter-individual response to this treatment, which limits aspirin efficacy in a significant fraction of patients. The utilization of inexpensive, naturally occurring flavonoids and other compounds present in purple grapefruit juice as a viable alternative to aspirin and other synthetic drugs as a viable and well tolerated pharmacotherapeutic protocol could have immediate widespread clinical benefits for many patients. The significance of the problem being addressed is a strength of the application.

2) APPROACH: The proposal is unusually well written and easy to read. It contains many strengths and few weaknesses. The application contains a clearly stated and testable hypothesis, with three specific aims designed to rigorously test the central hypothesis. These are major strengths of the application. The applicant will recruit 12 healthy volunteers to participate in a limited clinical trial of efficacy of acute and chronic consumption of purple grapefruit juice as an anti platelet aggregation agent, in comparison to aspirin as a positive control and white grape juice as a negative control. Preliminary data are presented to demonstrate the feasibility of the methodology and a power analysis is provided to support the

selection of population sample size to provide statistically significant data that can be utilized to support future applications for extramural funding from the American Heart Association and other state and federal agencies. The applicant proposes to conduct a well designed, randomized, single-blind crossover study to determine the efficacy of purple grape juice to reduce platelet aggregation. The crossover study design, inclusion of both positive and negative controls, and inclusion of sufficient patients to achieve statistical significance of the study results are also strengths of the application.

A number of minor weaknesses only modestly diminishes enthusiasm for this otherwise highly promising application. The rationale for the hypothesized ability of purple grape juice to therapeutically modify serum cholesterol and homocysteine levels (in addition to platelet aggregation) is weak, however this is only a secondary hypothesis and objective of the application. However, since the samples will be available from the primary aims of the project, conducting the additional serum analyses seems quite reasonable. Although a number of appropriate exclusion criteria are stated, the study population, while admirable in composition, may be too broad for the limited number of participants proposed. In particular, age and gender effects might be greater than anticipated and confound the interpretation of results. Also, since the most likely active agents in the grape juice are hypothesized to be flavonoids, which occur widely in many foods, normal subject diets may vary sufficiently to also possibly confound the results. The investigators might wish to consider requiring the study participants to exclude additional foods from their diet during their study, or at least keep detailed dietary logs. Given the half life of most naturally occurring compounds in the human body, the 4-week washout period may be unnecessarily long. Indeed, the investigators should consider measuring experimental serum parameters during the washout period, to begin to estimate the elimination kinetics of the flavonoids and the duration of flavonoid effects, as well as the estimated kinetics for onset of pharmacological effects that will be derived from the study design as proposed.

3) INNOVATION: The project seeks to develop preliminary information to support the development of a new pharmacotherapeutic intervention for cardiovascular and cerebrovascular disease. Utilization of natural products to achieve therapeutic goals is in itself not novel, nor is the use of flavonoids as chemotherapeutic agents and other investigators have suggested that purple grape juice might have anti platelet activity. The analytical methodologies proposed are state of the art, but not in of themselves innovative. Nonetheless the proposed studies address a highly significant problem and will generate useful new information with high potential for developing new or alternative therapeutic interventions for many human patients.

4) INVESTIGATOR: The applicant is an assistant professor in the Clinical Sciences Division of the UNM College of Pharmacy Program. He has held this position since 1997. To date he is listed as author of 8 peer reviewed manuscripts and four book chapters. The investigator does not appear to have yet been awarded any prior research support. The applicant does appear to be well trained and experienced in conducting small clinical trials similar to the one proposed in this application. He is also experienced in the laboratory techniques required for the proposed studies. Thus the applicant is well qualified to conduct the proposed experiments and recruited the support and collaboration of several senior basic and clinical scientists at UNM to serve as mentors and co-investigators for the proposed studies, engendering confidence that the proposed studies will be successfully completed. The training and experience of the investigative team is a strength of the application as is the participation of the

applicant in the GCRC Scholar Program and the formal mentoring program of the applicant with Dr. XXXXXXXXXXXXXXXXXXXX.

5) ENVIRONMENT: The research environment at the UNM College of Pharmacy and the UNM General Clinical Research Center are excellent and adequate and suitable for the proposed studies. All equipment and resources to be required for the proposed studies appear to be available to the investigators, or will be acquired from the budget requested for this project. Many senior scientists in the general area of drug metabolism and disposition are available to this junior investigator here at UNM to serve as consultants. The research environment and facilities of the UNM General Clinical Research Center available for this project are a strength of the application.

BUDGET: Budget is reasonable and adequate for the project as proposed. The applicant has obtained significant matching resources in terms of both supplies and clinical services, from the UNM General Clinical Research Center to support this application. The institutional support provided by the GCRC is also a strength of the application.

HUMAN SUBJECTS: OK – HRRRC Approval

VERTEBRATE ANIMALS: N/A

MINORITY, GENDER AND CHILDREN: OK