

Development of dietary polyphenol preparations for treating Veterans with Gulf War Illness

Presentation to the Gulf War Research Advisory Committee
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Presented by the **VA War Related Illness and Injury Study Center (WRIISC)**

Disclosures

- Department of Defense, Congressionally Directed Medical Research Program- GW130070
- Principal Investigator- Giulio Pasinetti, MD, PhD
- Co-Investigator- Lap Ho, PhD
- *"The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States government."*
- *"This material is the result of work supported with resources and the use of facilities at the War Related Illness and Injury Study Center at VA-New Jersey Health Care System, East Orange, NJ and VA Office of Public Health."*

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Rationale

- No established treatment for Gulf War Illness
- Flavonoids, a subclass of polyphenols, may help alleviate fatigue and cognitive dysfunction
- Innovative Treatment Evaluation Award
 - DoD CDMRP
 - Phase 1/2a randomized controlled trial

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Pathophysiology

- Alterations in brain connectivity (3)
- Alterations in brain metabolism (4)
- Dysfunction in the cholinergic autonomic system (5)
- Dysfunction in dopamine/glutamatergic neurotransmission (6)
- Inflammatory responses (7, 17, 18).

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Polyphenols

- Two or more benzene rings that each having at least one hydroxyl group (OH)
- abundant in fruits, vegetables, berries, tea, grapes and other plant sources
- potential health benefits, including
 - cancer prevention (8)
 - reducing the risk of heart disease (9)
 - protection against neurodegenerative disorders (10)

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Cognition

- **Preclinical**
 - Flavonoid subclass Concord purple grape juice (CGJ) effectively promote neuronal plasticity mechanisms that play a major role in learning and memory functions (11;12).
 - Bioavailable, bioactive, brain-penetrating
- **Clinical**
 - 16-weeks of dietary supplementation with CGJ (15 - 21 oz. per day) improved cognitive function of older adults with mild cognitive impairment (14)

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Fatigue & Inflammation

- Chocolate, which contains a high quantity of many flavonoids found in CGJ, significantly reduced subjects' self-reports of fatigue (15).
- Flavonoids are potent anti-inflammatory reagents (16).

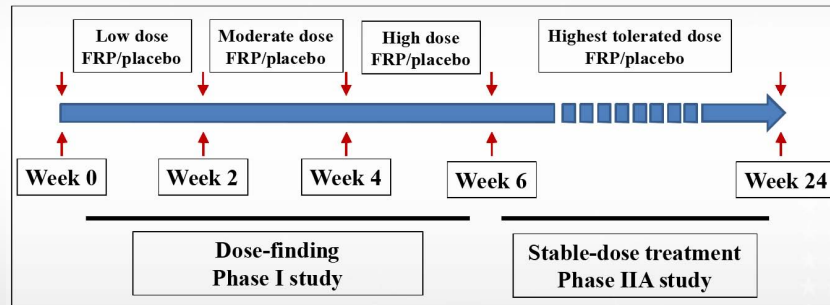
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Safety and Tolerability

- Two human studies (Krikorian (14)) and Novotney (unpublished) demonstrate no adverse effects of 16 oz CGJ daily.
- In both studies, the CGJ was well tolerated.

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Study Design



Primary Outcomes

- Compliance to CGJ/placebo treatment that will be monitored based on tabulation of returned unused juice.
- Safety/tolerance to CGJ/placebo treatment that will be monitored using a symptom checklist.
- Changes in cognitive functions based on assessments of neuropsychological battery (NPB).
- Changes in fatigue assessed using the self-report Chalder Fatigue Scale questionnaire.
- Plasma flavonoid profiles.

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Population- Inclusion Criteria

- Gulf War Veterans deployed to the Persian Gulf theatre between August 1990 and August 1991.
- GWI will be defined according to Steele et al. (27).
 - 6 symptom domains
 - Requires endorsement of moderately severe and multiple symptoms in at least 3 of those domains.
 - Each symptom first became problematic during or after the Gulf War.

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Population- Exclusion Criteria

- Conditions that might interfere with ability to report symptoms (e.g., drug use)
- Conditions that may explain the symptoms of GWI (e.g., diabetes, heart disease, among others)
- Significant current (e.g., suicidal or homicidal ideation) or lifetime psychiatric diagnoses (e.g., schizophrenia or bipolar disorder)
- Regular consumption of high levels of dietary polyphenol

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Sample Size

- 30 participants in each arm (randomized in blocks of four).
- Sample size determined based on need for feasibility/pilot data for larger study.
- Sample size (n=60) produces 80% power to detect a rare adverse event (incidence 2.5%) and 80% power to detect a 20% difference in the change in reaction time on the NES.

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Study Timeline

	Week	0	2	4	6	8	12	16	20	24
Recruitment	x									
Informed consent	x									
Dispense FRP/placebo	x	x	x	x	x	x	x	x	x	x
Collect empty bottle/log sheets	x	x	x	x	x	x	x	x	x	x
Food frequency questionnaire	x	x	x	x	x	x	x	x	x	x
Brief Symptom Inventory	x	x	x	x	x	x	x	x	x	x
Patient Health Questionnaire- 15	x	x	x	x	x	x	x	x	x	x
Neuropsychological Battery	x						x			x
Chalder Fatigue Scale Questionnaire	x						x			x
Alcohol, Smoking and substance use involvement screening test	x						x			x
Pittsburgh Sleep Quality Index	x						x			x
Post-Traumatic Stress Disorder	x						x			x
Patient Health Questionnaire – 8	x						x			x
Blood collection	x						x			x

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Neuropsychological Tests

- Attention, concentration & information processing
 - NES simple reaction time
 - NES symbol-digit substitution
 - NES serial digit learning
 - Paced Auditory Serial Addition Test (PASAT)
 - Wechsler Adult Intelligence Scale (WAIS-IV) digit span subtest
- Abstraction and conceptualization
 - Trail Making test
 - Halstead Category Test Short Form

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Data Analysis

- Summary of new/exacerbated symptoms(safety)
- Summary of adherence (tolerability)
- linear regression $\Delta Y \sim \beta_0 + \beta_1 \text{Group} + \beta_2 X$
 - ΔY is the change before and after treatment
 - Group denotes the treated/placebo status
 - X is the covariate vector, such as compliance, dose, blood flavonoid content, age, gender and dietary polyphenol intake outside of the therapy

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Impact

- Gather key information for a larger efficacy study of CGJ
 - Safety/tolerability
 - Dose
 - Outcomes
 - Covariates
- Explore efficacy
 - Few rigorous human studies of polyphenols
 - No accepted treatments for GWI

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