Strengthening Knowledge
and Understanding
of Dietary Supplements

Strengthening the Rigor and Reproducibility of Dietary Supplement Research

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Current DS Research Landscape

RESOURCES

- NIH research investment
- Various research reporting guidelines
- ODS program and NIH support for research reliability and translatability

CHALLENGES

- Translatable design and duration
- Numerous formulations and variable characterization
- Limited validated biomarkers
- Translatable health outcome measures
- Reporting transparency

STATE OF THE SCIENCE

- Heterogeneous biomedical literature and evidence base

Reproducibility and Integrity Guidance to Optimize Research (RIGOR) for Dietary Supplements (DS)

Informing, developing, & implementing ODS efforts to advance the DS research field

RIGOR Anticipated Outcomes

Identified topic areas in need of improved analytical characterization or methodological rigor

NIH resources and approaches to aid replicability, reproducibility, comparability, and translatability

Consolidated rigor and reproducibility best practices for DS research

RIGOR Activities & Deliverables

GOAL

- Modernize recommendations for DS and natural product characterization

APPROACH

- Update ODS product integrity guidance, expand to consider bioavailability

GOAL

- Identify research gaps and needs

APPROACH

- Portfolio analyses & literature reviews

GOAL

- Prioritize research, resource needs & opportunities

APPROACH

- Scientific workshops

ODS mission, cross-cutting themes, overarching goals

- Catalyze and initiate innovative dietary supplement (DS) research by coordinating across the Division and NIH
- Support development of cross-disciplinary research resources and training to build capacity for groundbreaking research
- A focus on improving population health and reducing risk of chronic disease
- Promote and support rigorous and reproducible biomedical science

NIH Dietary Supplements Research Portfolio (FY19-FY23)

Preliminary Estimates and Categorization by Studied Systems or Health Outcome

Broad Category*	Number of awards
Cellular, enzymatic or molecular mechanisms	489
Digestive and gastrointestinal system	317
Immune function	281
Cancer	239
Women's reproductive health	196
Nervous system	183
Cardiovascular system	158
Nutrient requirements / Metabolism	121
Pediatric topics	117
Aging	110
Diabetes	103
Cognitive performance	95
Obesity	78
Musculoskeletal system	75
Respiratory system	71
Vision	48
Addictions	46
Psychological health and behavior	45
Urinary system	45
Dietary supplement / Drug interactions	33

Sub-category*	Number of awards
Microbiome	221
Fetal development	134
Pregnancy	104
Inflammation	97
Immune modulation	77
Alzheimer's Disease	54
Colon cancer	54
Infant health	51
Type 2 diabetes	46
Gastrointestinal absorption / excretion	41
Liver disease / Cirrhosis	41
Breast cancer	40
Inflammatory Bowel Disease	36
Alcohol abuse	35
Growth	30
Hypertension / Blood pressure	29
Chronic Kidney Disease (CKD)	28
Insulin resistance	28
Prostate cancer	27
Bone mass / Bone density	26

**top 20 categories*

A Guiding Principle for Dietary Supplement Research

*The translation of data from studies examining the mechanisms and health effects of dietary supplements, to inform healthcare practices and individuals' decisions to use or avoid dietary supplements, requires a **rigorous evidence base** that is **reproducible** and **accurately reported** in the peer-reviewed literature.*

Building an Evidence Base for Health Outcomes: AREDS Example

Age-Related Eye Disease Studies (AREDS/AREDS2): major findings

The NEI conducted the Age-Related Eye Disease Study (AREDS) and the follow-on ARED study cataract and age-related macular degeneration (AMD). Study researchers tested whether taking nutritional supplements could prevent or slow these diseases. The formulations tested in the trials are now sold as the AREDS and the AREDS2 formulas.

Major AREDS/AREDS2 findings:

1. Taking AREDS or AREDS2 supplements reduces the risk progression from intermediate to advanced AMD by abo 25 percent
2. AREDS and AREDS2 supplements do not prevent AMD onset
3. AREDS and AREDS2 supplements do not have an effe cataract
4. Omega-3 fatty acid supplements do not have an effect cataract or AMD
5. Current and former smokers should take the AREDS2 formula and avoid the AREDS formula with beta-carot which increases lung cancer risk

Commercially available formulas based on AREDS/AREDS2

Nutrient	AREDS formula*	AREDS2 formula
Vitamin C	500 mg	500 mg
Vitamin E	400 IU	400 IU
Beta-carotene	15 mg	-
Copper (cupric oxide)**	2 mg	2 mg
Lutein	-	10 mg
Zeaxanthin	-	2 mg
Zinc	80 mg	80 mg

NIH study confirms benefit of supplements for slowing age-related macular degeneration

After 10 years, AREDS2 formula shows increased efficacy compared to original formula, benefit of eliminating beta-carotene

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AREDS/AREDS2 | Age-Related Macular Degeneration

Division of Epidemiology and Clinical Application

Supplements slow disease progression during late stage of "dry" age-related macular degeneration

New analysis shows benefit of taking AREDS2 formula in late AMD

festyle | Clinical Research | NEI

) have found that
progression of late-
with late-stage
scans of participants

DISEASES & CONDITIONS

Macular degeneration: Will a supplement cocktail slow it down?

Encouraging new findings suggest the AREDS2 formula might work even in late-stage dry AMD.

March 1, 2025

By ***Heidi Godman***, *Executive Editor, Harvard Health Letter*

https://www.nei.nih.gov/research/clinical-trials/age-related-eye-disease-studies-aredsareds2/about-areds-and-areds2
https://www.nei.nih.gov/about/news-and-events/news/nih-study-confirms-benefit-supplements-slowing-age-related-macular-degeneration
https://www.nei.nih.gov/about/news-and-events/news/supplements-slow-disease-progression-during-late-stage-dry-age-related-macular-degeneration
https://www.health.harvard.edu/diseases-and-conditions/macular-degeneration-will-a-supplement-cocktail-slow-it-down

Challenges to Reproducible & Translational DS Research

Dietary supplement studies excluded from analysis in systematic reviews and meta-analyses are often telling > frequent limitations in research comparability and translatability

"Antioxidant lipid supplements on cardiovascular risk factors"[1]

- Of 438 studies screened, 308 excluded for:
  - No randomization (n=97)
  - No relevant outcome (n=136)
  - Short intervention duration (n=24)
  - Included participants with severe disorders (n=51)

"Effectiveness of folate-based interventions on cognitive function in older adults"[2]

- Of 51 studies assessed:
  - 17 studies (33%) did not report baseline status
  - 14 studies (27%) had duration <6 months
  - 3 different combinations of folate / B12 / B6 included in summary assessment; dosage of folate-based interventions inadequately described

"Quality of evidence for efficacy of probiotics for rheumatoid arthritis"[3]

- Of 7 identified systematic reviews and meta-analysis (2017-2023) and assessing 21 outcomes:
  - All determined to have low or very low quality for methodology and evidence
  - Almost all included trials had issues in randomization, blinding, sample size, or follow-up

[1]S Wan et al. 2024. *Nutrients*. 16:2213. doi: 10.3390/nu16142213
[2]L Zhang et al. 2024. Nutrients. 16:2199. doi: 10.3390/nu16142199
[3]W Li et al. 2024. Front Immun. 15. doi: 10.3389/fimmu.2024.1397716

Reproducibility and Integrity Guidance to Optimize Research (RIGOR) for Dietary Supplements

- How can ODS continue and grow its efforts to improve the rigor and translatability of DS and related nutrition research within the focus areas of **Analytical Sciences** and **Research Methodology Capacity Building**?

- How can ODS further promote a more comparable and reproducible evidence base of mechanistic and clinical research?

- Where should future ODS resources and funding for DS analytical sciences and methodology capacity be prioritized?

➢ **Overall Goals - *expand ODS' tools and collaborative efforts to promote progress in the rigor with which DS research studies are designed and conducted, evaluated, and reported in the literature***

RIGOR for DS – Activities Initiated and Planned

Update and clarify ODS recommendations for characterizing the chemical composition of DS ingredients and products used as experimental/clinical interventions

- Partner with ICs to review the impact of natural product guidance for characterization on resulting DS research

Expand ODS portfolio analysis capabilities to assess NIH investment in DS research

- Collaborate with OPA to develop more informative assessments of NIH's DS investment portfolio

Characterize NIH-supported DS clinical research

- Assess landscape of methodological approaches, study designs, populations, and outcome measures

SM Pasiakos and AJ Kuszak. *Am J Clin Nutr*. 2025. https://doi.org/10.1016/j.ajcnut.2025.04.001

Updating and Clarifying ODS "Product Integrity" Guidance

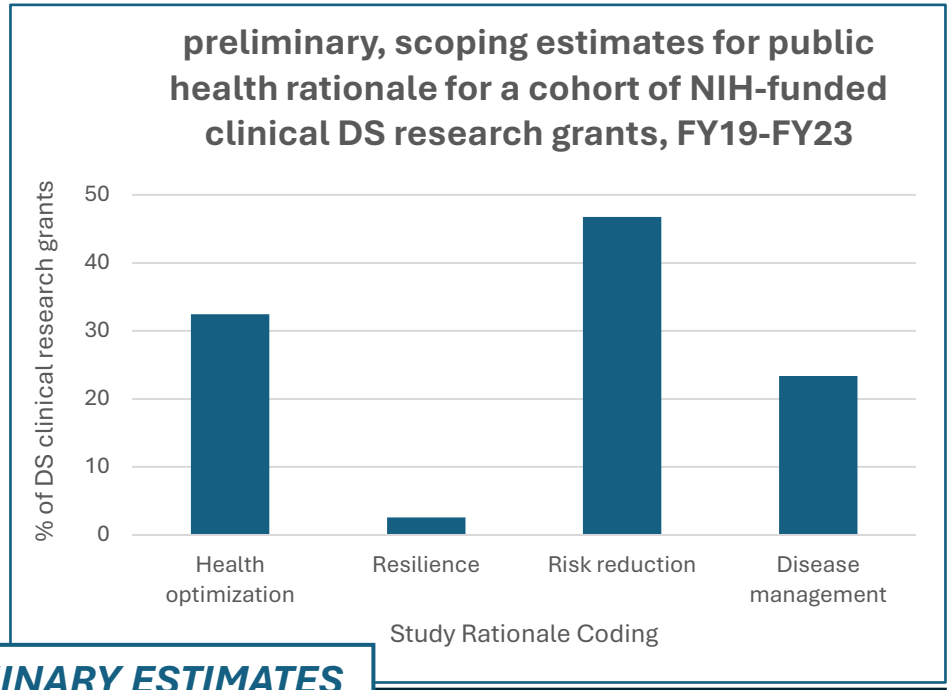
"…many studies of botanical natural products are carried out with poorly characterized study material, such that the results are irreproducible and difficult to interpret." - JJ Kellogg et al. Nat Prod Rep. 2019.

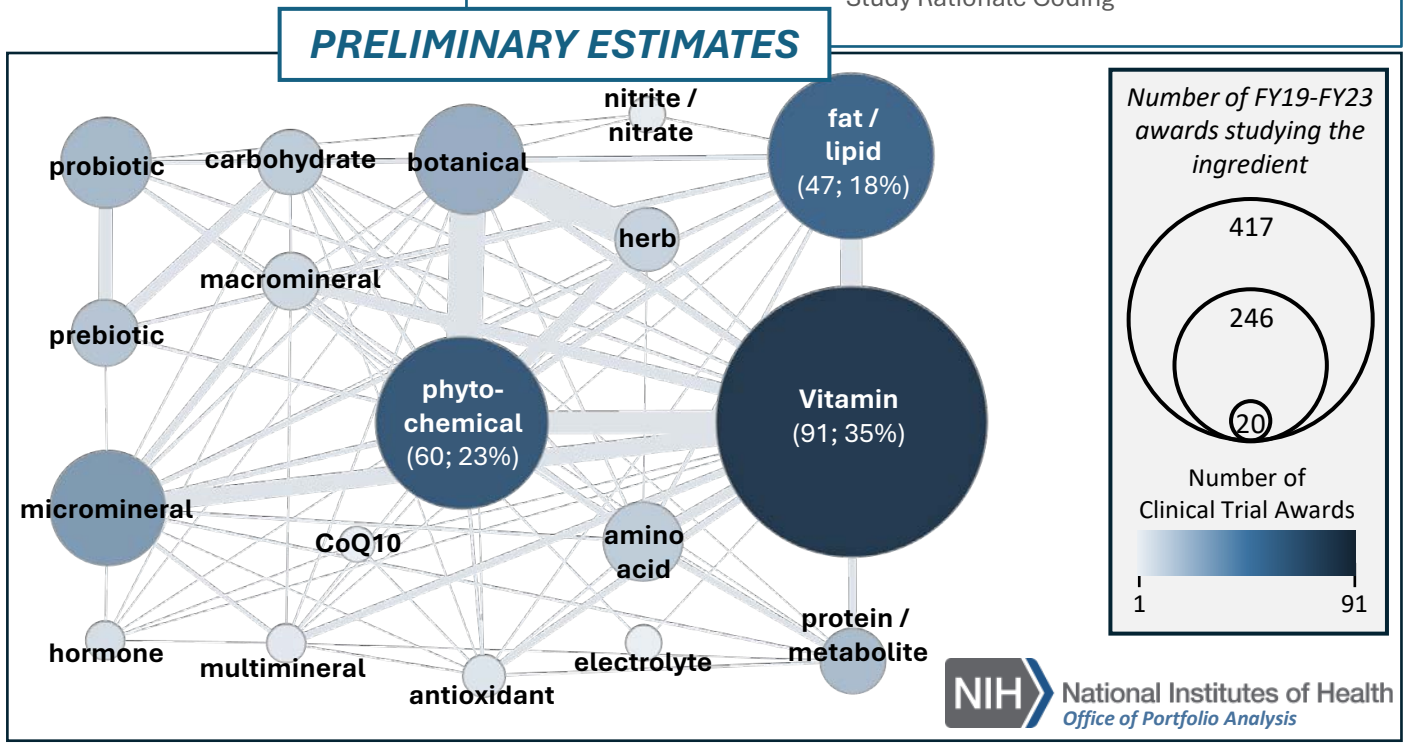
- Establish specifications for the intervention and demonstrate:
  - Identity and authentication
  - Chemical composition
  - Purity
  - Stability
  - Reproducible preparation
  - Considerations for bioavailability

https://ods.od.nih.gov/Funding/ProductQualityResources.aspx#improve
https://ods.od.nih.gov/Funding/FundingFAQ.aspx#information

Characterizing NIH Investment in DS Clinical Research

- To what extent is there a focus on health optimization and chronic disease prevention?
- Which ingredients (and combinations) are studied for different conditions, and are there emerging opportunity areas?
- Are the study designs optimal for a reproducible and translatable evidence base?
  - Experimental models?
  - Duration and time points?
  - Subject demographics and baseline measures?
  - Outcome measures?





RIGOR for DS – Deliverables & Goals

- Identify approaches to promote more rigorous characterization and increased reproducibility of DS interventions
- Identify topic area and methodological needs, emerging resource development opportunities

➢ Develop consolidated best practice recommendations for the design, conduct, and reporting of DS research

➢ Stimulate enhanced replicability, reproducibility, and translatability of DS research

➢ Promote a robust evidence-base of high-quality research on the health effects of dietary supplement ingredients and products

NIH National Institutes of Health
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Thank you!

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