Synergism, Antagonism or Additivity of Dietary Supplements

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Problems Inherent in Published Literature
Drugs 36: 83-110.

- Literature over-populated.
- Case-Reports: relevant but anecdotal.
- Lab/Clinical Study: controlled, but questionable relevance & general applicability.
- Terminology used ambiguously; incorrectly.
  - "interaction," "synergism," "potentiation"
  - "No-Interaction" concept sorely lacking
- Data quality poorly evaluated.

Drug–Dietary Supplement Interaction Literature Sources
- Case Reports
- Clinical Studies
- Laboratory Studies

Data Evaluation
- Clinical & Laboratory Studies
  - Data Quality Assessment Depends on Objectives
  - Prediction & Clinical Management
    - Validate interaction.
    - Generalize & define patient conditions.
    - Direction & type of interaction.
    - Magnitude of interaction.
    - Variance / confidence intervals.
    - Mechanism of interaction.
    - Incidence (post-marketing surveillance).

Interactions

Synergism
- More response / less drug than expected.
  - Extrinsic, NOT Intrinsic
  - Dependent Upon the “Expected” Effect.
  - Highly Dependent Upon Dose AND Ratios.
  - Quantitative, not Qualitative.
  - Dose-Response, not Mechanism
  - Mathematical, not Biological

Antagonism
- Less response / more drug than expected.

Loewe Additivity [Dose Additivity]
- No self-interaction
- Agents act as simple dilutions (potency)
- Sum doses & potencies of each agent
  - \( D_A + D_B = D_{A+B} \)

Bliss Independence [Response Additivity]
- Statistical independence
- Relative effect of A not influenced by B
- Sum effects of each agent
  - \( E_{A+B} = E_A + E_B - (E_A \times E_B) \)

What is “Expected”? 2 Classical Models for Non-Interaction
**Impact of the No-Interaction Model**

- D(a)  
- D(b)  
- D(c)  
- R (a + b + c)  

**Criteria for Evaluating Interaction Studies**

1. Dose-response curves for the mixture components should be adequately characterized.
2. An appropriate “no-interaction” hypothesis should be explicitly stated and used as the basis for assessing synergy and antagonism.
3. Combinations of mixture components should be assessed across a sufficient range to support the goals of the study.
4. Formal statistical tests should be used to distinguish interaction from non-interaction.
5. Interactions should be assessed at relevant levels of biological organization.


**Algorithm for Applying Criteria**

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<th>Criterion</th>
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<th>C</th>
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<tr>
<td>Satisfies Criterion</td>
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- Does not weight individual criteria.
- Does not evaluate clinical relevance.
- Apply cautiously to mechanistic & p'kinetic studies.
- Challenging for whole animal or clinical studies.

**Applying the Criteria Ginkgo**

Steinke et al., 1993: Ginkolides A + B synergistically inhibit platelet aggregation.

1. Full dose-response characterization of ginkolides A and B.
2. Dose-addition defined as no-interaction hypothesis.
3. Tested 7 combinations at 50% inhibitory effect.
4. Applied formal statistical procedure to test differences between observed and expected (dose-additive) effects (Concave Isobole).
5. Assessed interaction at interpretable level of biological organization.

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Applying the Criteria
Kangen Karyu (KGK)

- KGK increases warfarin AUC at 2 g/kg, but not at 0.5 g/kg in rats.
- KGK has no effect on PT at any dose tested in rats.
- 0.2 g/kg and 0.5 g/kg + 1 mg/kg warfarin increased bleeding time above warfarin alone by 20% and 25%, respectively.
- “Since KGK and warfarin synergistically exhibit antithrombotic effects, their combination would be therapeutically valuable.”

Makino et al., 2002 (lab study in rats)

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-KKG alone inhibits platelets; increases bleeding time in mice.

Applying the Criteria
American Ginseng

Duda et al., 1999: American ginseng and breast cancer therapeutic agents synergistically inhibit MCF-7 cancer cell growth.

<table>
<thead>
<tr>
<th>RX</th>
<th>Cell Survival</th>
<th>Expected Effect (?)</th>
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<tbody>
<tr>
<td>TAM (1E-6M)</td>
<td>87%</td>
<td>(.87) x (.80) = (.696) survival</td>
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<tr>
<td>TAM (1E-5M)</td>
<td>10%</td>
<td>(.13) + (.20) = .33 cell death</td>
</tr>
<tr>
<td>AG (60mg)</td>
<td>90%</td>
<td>67 survival</td>
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<tr>
<td>AG (80mg)</td>
<td>85%</td>
<td></td>
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<tr>
<td>AG (100mg)</td>
<td>80%</td>
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<td>TAM + AG (100mg)</td>
<td>75%</td>
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Criterion 1 2 3 4 5 T C
Score .5 0 0 0 0 0 0.1

Observations / Recommendations / Challenges

- Synergism / antagonism useful information for specific drug combination therapies.
  - Apply sound methodologies - difficult but still important for clinical study designs.
  - Magnitude, direction and variability of interaction may be important for appropriate clinical management.
- Focus on clinical significance of interactions
  - Intra-individual variations in drug levels with fluctuations in diet, sleep, stress, activity level, etc.
- Efficient Study Designs Needed for Clinical Studies.