NUCOREBIO · FORMULATION INTELLIGENCE SERIES

Synergy & Incompatibility Matrix

Which Ingredient Combinations Amplify Each Other — and Which to Avoid

Ingredient synergy — where combined biological effects exceed the sum of individual contributions — is the formulator's highest-value tool. True synergy requires complementary mechanisms: two ingredients acting on the same pathway produce additive effects at best; two ingredients acting on different but convergent pathways produce synergistic effects. Conversely, mechanism-blind combinations can produce interference, antagonism, or safety risks that undermine formula integrity. This reference matrix documents NuCoreBio R&D;'s curated evidence base for synergistic pairs and problematic combinations across major categories.

READING GUIDE

How to read this matrix: SYNERGISTIC = combined effect > sum of individual effects (mechanistic rationale + at least one in vivo study or strong mechanistic evidence). ADDITIVE = effects sum linearly; no interaction. INTERFERENCE = one ingredient reduces effectiveness of the other. ANTAGONIST = ingredients directly oppose each other's mechanism. SAFETY CONCERN = combination creates potential adverse effect risk.

— MATRIX 01

Testosterone & Male Performance — Synergy Map

The male performance category has the richest evidence base for combination effects. Understanding the multi-axis nature of testosterone regulation reveals why single-ingredient products are inherently less effective than properly designed stacks.

Combination	Interaction Type	Mechanism of Synergy / Antagonism	Evidence Strength	Practical Recommendation
Tongkat Ali + Ashwagandha	SYNERGISTIC ★★★★★	TKA: HPG axis stimulation (LH↑, T production). ASH: Cortisol suppression removes T-blocking stress signal. Dual-axis approach: T synthesis + T preservation	Multiple RCTs on each + mechanistic synergy confirmed	Core combination of any male T formula. Stack at full doses of each (not reduced)
Tongkat Ali + Fenugreek	SYNERGISTIC ★★★★■	TKA: Increases T production. Fenugreek: Reduces SHBG binding → converts more total T to free T. Complementary: more T produced AND more T available for receptor binding	Strong mechanistic evidence; both RCT-validated individually	Excellent stack. Consider adding Zinc for synthesis cofactor completeness
Ashwagandha + Zinc	ADDITIVE→ SYNERGISTIC ★★★★■	ASH: Reduces cortisol (removes T suppression). Zinc: Essential cofactor for testosterone synthesis enzyme (17β-HSD). Both act on different rate-limiting steps	Strong mechanistic; RCTs for each; combination not RCT-tested	Always include Zinc in any T formula. Use bisglycinate form at 25–30 mg
D-Aspartic Acid + TKA	ADDITIVE ★★★■■	DAA: Stimulates LH release from anterior pituitary. TKA: Also stimulates LH via different receptor pathway. Same endpoint (LH) but different upstream activation. Not synergistic — additive	DAA RCT evidence weaker than TKA; modest additional benefit	Optional addition. TKA alone is more evidence-backed; DAA adds modest LH stimulation
Boron + TKA + Fenugreek	SYNERGISTIC ★★★★■	Boron: Reduces SHBG levels directly (reduces synthesis). Fenugreek: Inhibits SHBG binding affinity. TKA: Increases T production. Triple complementary axis: more T + less SHBG + reduced SHBG binding capacity	Boron RCT (Naghii 2011) + mechanistic; others RCT-validated	Premium male formula stack. Boron at 6–10 mg activates SHBG reduction axis

Combination	Interaction Type	Mechanism of Synergy / Antagonism	Evidence Strength	Practical Recommendation
High-Dose Zinc + Copper (absent)	SAFETY CONCERN ■■	Zinc >25 mg/day suppresses copper absorption by competing for intestinal metallothionein. Prolonged zinc supplementation without copper causes copper deficiency (anemia, neurological effects)	Well-established nutritional interaction	Always include Copper 1–2 mg when zinc ≥25 mg/day is used. Copper bisglycinate preferred
Tribulus Terrestris + TKA	REDUNDANT / INTERFERENCE ★★■■■	Tribulus's claimed mechanism (saponins → LH elevation) is unsupported by RCT data in healthy males. Does not add to TKA's documented HPG stimulation. Wastes formula space and increases cost	Tribulus RCT data negative in eugonadal men (multiple studies)	Do not include Tribulus in professional formulas. Replace with Fenugreek or Boron for evidence-based SHBG reduction
High-Dose DAA (>3g) + Testosterone	ANTAGONIST at high dose ★★■■■	At doses >3g/day DAA, preclinical evidence shows paradoxical androgen receptor downregulation. Testosterone elevation may trigger negative feedback	Animal data primary; cautionary for human formulas	Keep DAA ≤3g/day. Higher doses not clinically validated and may be counterproductive

— MATRIX 02

Cognitive / Nootropic — Synergy Map

Cognitive formulas benefit enormously from layered mechanisms: acute fast-onset actives combined with chronic neuroplasticity agents create stacks where consumers feel effects immediately AND build cognitive capacity over time.

Combination	Interaction Type	Mechanism	Evidence	Recommendation
Alpha-GPC + Lion's Mane	SYNERGISTIC ★★★★★	Alpha-GPC: Acute ACh precursor → immediate cognitive boost. Lion's Mane: Chronic NGF upregulation → long-term neuroplasticity. Acute + Chronic axis: immediate performance + structural improvement	Strong: both RCT-validated; mechanism complementarity confirmed	Gold standard nootropic stack. Alpha-GPC 300mg + Lion's Mane 500mg (dual extract) as minimum
L-Theanine + Caffeine	SYNERGISTIC ★★★★★	Theanine: Promotes alpha-wave activity; reduces caffeine-induced anxiety and jitteriness. Caffeine: Adenosine antagonism → alertness. Combined: clean focused energy without anxiety. Most validated combination in cognitive supplementation	Multiple DB-RCTs confirming synergy (Owen et al., 2008; Haskell et al., 2008)	Classic combination. 2:1 ratio (Theanine:Caffeine) optimal. 200mg Theanine + 100mg Caffeine per serving
Bacopa + Alpha-GPC	SYNERGISTIC ★★★★■	Bacopa: AChE inhibition → preserves ACh in synapse. Alpha-GPC: Increases ACh synthesis. Combined: more ACh produced AND less degraded = significantly elevated cholinergic tone	Strong mechanistic; individual RCTs validated; combination logical and widely used	Core memory stack. Both at full clinical doses (not split/reduced)
Phosphatidylserine + Alpha-GPC	ADDITIVE→ SYNERGISTIC ★★★★■	PS: Cell membrane integrity + cortisol reduction → neuroprotection. Alpha-GPC: Cholinergic precursor. PS improves membrane quality, enhancing receptor function for ACh signaling	Good mechanistic evidence; PS RCTs independent; combination used in clinical memory programs	Memory-focused stack. PS 100–300mg + Alpha-GPC 300mg

Combination	Interaction Type	Mechanism	Evidence	Recommendation
Hericenones + Erinacines (Lion's Mane dual extract)	SYNERGISTIC ★★★★★	Hericenones: Peripheral NGF synthesis stimulation. Erinacines: Central CNS NGF (BBB-permeable). Dual pathway = complete NGF upregulation (both peripheral and central systems)	Mechanistic synergy established (Lai et al., 2013)	Always specify DUAL extract. Single fruiting body or single mycelium extract misses one mechanism entirely
Citicoline + Uridine	SYNERGISTIC ★★★★■	CDP-choline (citicoline) provides choline + cytidine. Uridine converts to UTP, combines with choline to produce PC (phosphatidylcholine) for membrane synthesis. Combined: superior membrane phospholipid synthesis vs. either alone	Strong mechanistic; supported by Cunnane et al. research	Premium nootropic stack for aging consumers. Citicoline 250mg + Uridine 250mg
High-Dose Choline + B5 (absent)	INTERFERENCE ★★★■■	Pantothenic acid (B5) is the cofactor for CoA, required for acetyl-CoA production in ACh synthesis. Without B5, additional choline cannot be efficiently converted to ACh	Nutritional biochemistry; widely accepted	Include B5 (pantothenic acid) 20–50mg in all high-dose cholinergic formulas
Bacopa + Iron / Copper	POTENTIAL INTERFERENCE ★★★■■	Bacosides show metal chelating activity. Co-administration with iron or copper supplements may reduce bioavailability of both	In vitro chelation data; human significance unclear	Separate dosing by 2+ hours if iron/copper co-supplementation

— MATRIX 03

Anti-Aging & Collagen — Synergy Map

Combination	Type	Mechanism	Evidence	Recommendation
Marine Collagen Tripeptide + Vitamin C	SYNERGISTIC ★★★★★	Gly-Pro-Hyp tripeptides stimulate fibroblast pro-collagen synthesis. Vitamin C is the cofactor for prolyl hydroxylase and lysyl hydroxylase — the enzymes that cross-link collagen fibers. Without Vit C, collagen chains cannot be hydroxylated → structurally weak collagen produced	Fundamental biochemistry; both ingredients RCT-validated; combination essential	Non-negotiable combination. Always include 250–500mg Vit C with collagen formulas
MCT Collagen + Hyaluronic Acid	SYNERGISTIC ★★★★■	Collagen: Restores dermal collagen matrix. HA: Dermal hydration and water retention in extracellular matrix. Combined: restored matrix structure + optimized hydration = synergistic improvement in skin firmness and elasticity	Both RCT-validated; combination logic strong; Proksch 2014 combined both	Core beauty stack. MCT collagen + HA (low MW, <300kDa) + Vit C
Astaxanthin + Collagen	SYNERGISTIC ★★★★■	Astaxanthin: Powerful antioxidant (500× > Vit E) + photoprotection reduces UV-induced MMP-1 collagen degradation. Collagen: Rebuilds what UV has degraded. Combined: synthesis supported + degradation prevented	Both RCT-validated; protection + synthesis dual axis	Premium anti-aging stack. Astaxanthin 4–8mg + MCT collagen 2500–5000mg
NMN + Resveratrol	SYNERGISTIC ★★★★■	NMN: Restores NAD+ levels. Resveratrol: SIRT1 activator. SIRT1 requires NAD+ as substrate. Combined: more substrate (NAD+) + activated enzyme (SIRT1) = amplified sirtuin activity vs. either alone. David Sinclair's most-cited longevity combination	Mechanistic synergy confirmed; human NMN RCT (Yoshino 2021); resveratrol bioavailability is the limiting factor	NMN 500mg + Resveratrol 100–200mg (phytosome form for BA). Add TMG 500mg for methyl donor balance
NMN + TMG (Trimethylglycine)	SYNERGISTIC ★★★★★	NAD+ biosynthesis from NMN consumes methyl groups. Without methyl donors, sustained NMN supplementation can deplete SAM (S-adenosylmethionine), impairing methylation reactions (DNA repair, neurotransmitter synthesis). TMG replenishes methyl pool	Strong mechanistic; essential co-administration	Always include TMG 500mg when NMN ≥250mg/day is used

Combination	Type	Mechanism	Evidence	Recommendation
High-dose Astaxanthin + Vitamin E	POTENTIAL ANTAGONISM ★★★■■	At very high doses, both astaxanthin and alpha-tocopherol compete for the same lipid peroxidation site. At standard supplement doses (4–12mg astaxanthin + ≤400 IU Vit E) this is clinically irrelevant. Only relevant at astaxanthin >40mg/day	In vitro competition data; not clinically significant at standard doses	Standard doses: no concern. Only relevant at very high astaxanthin doses (rarely used)

— MATRIX 04

Immune & Longevity — Synergy Map

Combination	Type	Mechanism	Evidence	Recommendation
Reishi + Turkey Tail (PSK)	SYNERGISTIC ★★★★■	Reishi: Bidirectional immunomodulation (NK cell activation + anti-inflammatory Th1 polarization). Turkey Tail PSK: T-cell and B-cell activation, NK augmentation through different PRR receptor subtypes. Different β-glucan structures → non-redundant immune activation	Mushroom immunology research; PSK clinical data in oncology support	Mushroom immune stack. Reishi 500mg + Turkey Tail 500mg (both dual extract, ≥30% polysaccharides)
Beta-1,3/1,6-D-Glucan + Zinc	SYNERGISTIC ★★★★■	Beta-glucan: Activates macrophages and NK cells via Dectin-1 receptor. Zinc: Essential cofactor for thymulin (thymic hormone) and T-cell receptor signaling. Both required for full innate + adaptive immune activation	Strong mechanistic; both RCT-validated individually	Core immune stack. Beta-glucan 250mg + Zinc bisglycinate 25mg
Quercetin + Zinc (ionophore effect)	SYNERGISTIC ★★★★★	Quercetin acts as a zinc ionophore — it carries zinc ions across the cell membrane into the intracellular compartment. Intracellular zinc inhibits RNA-dependent RNA polymerase of RNA viruses. Quercetin + Zinc = dramatically enhanced intracellular antiviral mechanism vs. either alone	Mechanistic confirmed; became widely recognized during COVID-19 research (Colunga et al., 2020)	Critical immune combination. Quercetin 500mg (EGCG also ionophore) + Zinc bisglycinate 25–30mg
EGCG (Green Tea) + Quercetin	SYNERGISTIC ★★★★■	Both are zinc ionophores (different binding affinities). Both inhibit NF-κB pro-inflammatory pathway (different binding sites). Both have antioxidant activity via different mechanisms. True molecular complementarity	Multiple in vitro studies; pharmacological modeling supports	Anti-inflammatory longevity combo. EGCG 300mg + Quercetin 500mg
NR/NMN + Pterostilbene (vs Resveratrol)	SYNERGISTIC ★★★★■	Pterostilbene (methylated resveratrol) has 4× longer half-life and superior BBB penetration vs resveratrol. Both activate SIRT1. Pterostilbene + NR: longer-duration sirtuin activation per dose	Pterostilbene pharmacokinetics superior (Remsberg 2008); SIRT1 activation confirmed	Consider pterostilbene (50–100mg) as upgrade from resveratrol in premium longevity formulas

Combination	Type	Mechanism	Evidence	Recommendation
Astragalus + Vitamin D3	ADDITIVE ★★★★■	Astragalus: Telomere protection (telomerase activator) + immunoadaptogen. Vitamin D3: Immune cell differentiation, innate immunity, anti-inflammatory (VDR-mediated). Complementary mechanisms across immune aging pathways	Both RCT-validated; combination logical	Longevity immune formula. Astragalus 500mg + D3 3000–5000 IU
High-Dose Beta-Glucan + Autoimmune Conditions	SAFETY CONCERN ■■	Beta-glucan is a potent immune stimulant. In autoimmune diseases (lupus, RA, MS, IBD), stimulating the immune system can exacerbate symptoms and trigger flares	Immunology consensus; contraindication in clinical practice	Contraindicate beta-glucan and strong immune stimulants in autoimmune disease. Label clearly

— MATRIX 05

Cross-Category Safety Interactions — Critical Reference

The following interactions cross ingredient categories and represent the safety-critical combinations that formulators must be aware of. These are the interactions most commonly missed when building complex multi-ingredient stacks.

Ingredient A	Ingredient B / Drug	Interaction Type	Mechanism	Risk Level	Action Required
Berberine (≥500mg)	Metformin / any hypoglycemic	Additive → Hypoglycemia Risk	Both lower blood glucose via AMPK; additive effect may exceed safe range	HIGH ■■	Require physician supervision; warn on label
Berberine (≥500mg)	Cyclosporine	Drug Level Increase	CYP3A4 inhibition raises cyclosporine AUC 2×	HIGH ■■	Contraindicate or require physician approval
Piperine (≥20mg)	Any CYP3A4-metabolized drug	Drug Level Increase	CYP3A4 and P-gp inhibition	MODERATE ■■	Warn about drug interactions; keep dose ≤10mg in consumer formulas
Zinc (>25 mg/day)	Copper (absent)	Copper Deficiency	Competitive intestinal absorption via metallothionein	MODERATE ■■	Always include 1–2mg copper in high-zinc formulas
High-dose Omega-3 (>3g EPA+DHA)	Anticoagulants (warfarin)	Anticoagulant potentiation	Additive antiplatelet and anticoagulant effect	MODERATE ■■	Warn about pre-surgical use and anticoagulant co-use
Valerian + Melatonin	Benzodiazepines / sedatives	Additive CNS Depression	Both enhance GABA/sleep pathways; additive sedation with prescription CNS depressants	MODERATE ■■	Include sleep formula warning for sedative co-use
Ashwagandha + Thyroid medication	Levothyroxine	Potential T3/T4 Increase	Ashwagandha modestly increases T3/T4; additive with levothyroxine	LOW-MODERATE	Flag for thyroid medication users; monitor TSH
High-dose Vitamin D3 (>5000 IU)	Vitamin K2 (absent)	Hypercalcemia / Calcification Risk	D3 increases calcium absorption; K2 (MK-7) directs calcium to bone, away from arteries. Without K2, excess calcium can deposit in soft tissue	MODERATE ■■	Always combine D3 >2000 IU with K2 MK-7 90–180mcg
Iron supplements	Green Tea (EGCG)	Iron Absorption Inhibition	Polyphenols form insoluble iron-polyphenol complexes in gut	LOW-MODERATE	Separate iron and green tea/EGCG dosing by 2+ hours

Ingredient A	Ingredient B / Drug	Interaction Type	Mechanism	Risk Level	Action Required
NMN/NR (>500mg)	TMG (absent)	Methyl Donor Depletion	NAD+ synthesis consumes methyl groups; risk of SAM depletion affecting DNA methylation	LOW-MODERATE	Co-administer TMG 500mg with NMN/NR ≥500mg/day

— MASTER FORMULAS

NuCoreBio Recommended Synergistic Stacks

Based on the synergy matrix above, the following stacks represent mechanistically optimized combinations — each ingredient chosen for a specific biological role, with no redundancy and maximum synergistic amplification.

Stack Name	Formula (Dose)	Mechanism Coverage	Expected Outcome Timeline
Premium Male Performance	TKA 300mg (200:1) + ASH 600mg (5% WIT) + Fenugreek 500mg (50% SAP) + Boron 10mg + Zinc 25mg + D3 3000IU	HPG stimulation (TKA) + Cortisol suppression (ASH) + SHBG reduction (FEN+Boron) + T synthesis cofactors (Zinc+D3)	2 weeks: Cortisol reduction. 4 weeks: Free T increase. 8 weeks: Peak total T elevation
Advanced Nootropic	Lion's Mane 750mg (dual ext) + Bacopa 300mg (45% BAC) + Alpha-GPC 300mg + Citicoline 250mg + L-Theanine 200mg + Caffeine 100mg	Acute ACh boost (Alpha-GPC) + Chronic AChE inhibition (Bacopa) + NGF induction (Lion's Mane) + Membrane synthesis (Citicoline) + Focus quality (Theanine+Caffeine)	Day 1: Acute focus (Theanine+Caffeine+Alpha-GPC). Week 2–4: Memory consolidation. Week 6–8: Neuroplasticity benefits
Premium Longevity	NMN 500mg + Resveratrol 150mg (phytosome) + TMG 500mg + Quercetin 500mg + D3 3000IU + K2 MK-7 180mcg + Astaxanthin 8mg	NAD+ restoration (NMN) + Sirtuin activation (Resveratrol) + Methyl balance (TMG) + Zinc ionophore antiviral (Quercetin) + Bone+immune (D3+K2) + Photoprotection (ASX)	4 weeks: Metabolic improvement. 8 weeks: Cellular energy. 12+ weeks: Epigenetic benefits
Beauty From Within	MCT Collagen 5000mg + HA (low MW) 120mg + Vit C 500mg + Astaxanthin 6mg + Biotin 5000mcg + Silica 50mg	Pro-collagen synthesis (Collagen+VitC) + Dermal hydration (HA) + UV protection + MMP inhibition (ASX) + Keratin synthesis (Biotin) + Collagen cross-linking (Silica)	4 weeks: Hydration improvement. 8 weeks: Skin elasticity. 12 weeks: Wrinkle depth reduction
Mushroom Immune Complex	Reishi 500mg + Turkey Tail 500mg + Lion's Mane 500mg (all dual extract) + Beta-Glucan 250mg + Quercetin 500mg + Zinc 25mg	Bidirectional immunomodulation (Reishi) + T-cell activation (Turkey Tail PSK) + NGF (Lion's Mane) + PRR activation (Beta-Glucan) + Zinc ionophore (Quercetin+Zinc)	2 weeks: NK cell activation. 4 weeks: Adaptive immunity enhancement. 8 weeks: Full immunomodulation + cognitive benefit

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