PHYTOFORGE-X^{TM} PhytoIntelligence Evidence-to-Formulation Research and Optimization Framework

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Abstract

PHYTOFORGE-X^{TM} is a reproducible, AI-executable research architecture for moving from **plants → bioactive molecules → mechanisms → evidence → safety constraints → combination hypotheses → laboratory validation**.

The system is designed for applications such as Alzheimer's disease, type 2 diabetes, glioblastoma, other cancers, inflammatory disorders, metabolic diseases, neurodegeneration, and other scientifically defined targets.

The framework deliberately separates:

1. chemical identity,
2. biological mechanism,
3. experimental evidence,
4. pharmacokinetics,
5. blood-brain-barrier feasibility,
6. toxicity,
7. drug-interaction risk,
8. combination synergy,
9. translational evidence,
10. and clinical evidence.

No preclinical observation may be promoted to a clinical claim.

The output is a ranked **research hypothesis set**, not a prescription.

1 Core Scientific Principle

The central PHYTOFORGE-X hypothesis is:

> A rationally selected combination of chemically characterized plant-derived molecules may produce useful multi-target biological effects when the individual components have complementary, experimentally demonstrated mechanisms, compatible exposure characteristics, acceptable laboratory safety profiles, and measurable combination synergy.

This hypothesis must be tested experimentally.

It must never be represented as established clinical efficacy merely because individual compounds have positive cell-culture, animal, observational, or mechanistic evidence.

For cancer applications, the framework must additionally distinguish:

- tumor-cell killing,
- tumor-cell selectivity,

- cancer-stem-cell effects,
- invasion/migration,
- angiogenesis,
- treatment resistance,
- DNA-repair effects,
- blood-brain-barrier exposure,
- and toxicity toward normal neural tissue.

2 Terminology

Plant-derived molecule A chemically defined compound originating from a plant or plant-associated natural product.

Candidate A molecule surviving the initial identity and evidence filters.

Mechanistic evidence Experimental evidence showing that a molecule changes a biological target, pathway, phenotype, or endpoint.

Predicted mechanism A mechanism inferred from docking, molecular modeling, network pharmacology, QSAR, AI prediction, or analogy but not sufficiently experimentally demonstrated.

Preclinical evidence Evidence obtained from biochemical, cellular, organoid, ex-vivo, animal, pharmacokinetic, or related experimental systems.

Clinical evidence Evidence obtained from human clinical research.

Combination hypothesis A proposed laboratory combination requiring experimental validation.

Formulation For PHYTOFORGE-X, a laboratory research combination. It does not mean an approved pharmaceutical product.

Hard exclusion A property that removes a candidate regardless of its biological activity score.

3 Required Input

Every PHYTOFORGE-X execution begins with:

```
DISEASE_OR_TARGET:
PRIMARY_DISEASE:
SECONDARY_DISEASES:
PRIMARY_BIOLOGICAL_OBJECTIVE:
TARGET_POPULATION:
EVIDENCE_CUTOFF_DATE:
NUMBER_OF_MOLECULES:
NUMBER_OF_FINAL_COMBINATIONS:
CLINICAL_TRANSLATION_ALLOWED: NO
HUMAN_DOSING_ALLOWED: NO
SELF_MEDICATION_ALLOWED: NO
```

Example:

```
DISEASE_OR_TARGET = Glioblastoma
PRIMARY_DISEASE = Glioblastoma multiforme
NUMBER_OF_MOLECULES = 100
NUMBER_OF_FINAL_COMBINATIONS = 5
EVIDENCE_CUTOFF_DATE = YYYY-MM-DD
```

4 AI Execution Contract

Any AI research engine receiving this specification shall execute the following sequence without silently skipping stages:

[$\boxed{P \rightarrow M \rightarrow E \rightarrow S \rightarrow I \rightarrow R \rightarrow C \rightarrow F \rightarrow V}$]

where:

P = Plant discovery M = Molecule identification E = Evidence extraction S = Safety analysis I = Interac

The AI must never jump directly from:

[plant $\rightarrow$ pill]

without passing through the evidence, safety, pharmacology, and combination-analysis layers.

5 Literature Search Architecture

The search system shall use multiple independent information sources whenever available.

Minimum recommended sources:

1. PubMed/MEDLINE
2. PubMed Central
3. Europe PMC
4. Crossref
5. Google Scholar or equivalent broad scholarly search
6. ClinicalTrials.gov or equivalent trial registry
7. FDA/EMA/Health Canada regulatory databases where relevant
8. DrugBank or equivalent interaction resource where legally and technically accessible
9. ChEMBL
10. PubChem
11. WHO/IARC resources where applicable
12. toxicology databases
13. authoritative pharmacology databases

Search methodology shall follow reproducibility principles associated with PRISMA and PRISMA-S. Full search strings, databases, platforms, dates, filters, and result counts should be retained. PRISMA-S specifically emphasizes reporting the database/platform, exact search strategy, dates, and reproducible search details. [1]

6 Universal Search Query Generator

The AI shall construct searches using the following conceptual Boolean architecture:
[D $\wedge(P_1 \vee P_2 \vee \cdots P_n) \wedge (M_1 \vee M_2 \vee \cdots M_n)$]
where:

- D = disease/target terms
- P = plant/natural-product terms
- M = mechanism terms

The generic PubMed query shall begin with:

```
(
\DISEASE"[Title/Abstract]
OR \DISEASE SYNONYM"[Title/Abstract]
OR \DISEASE SUBTYPE"[Title/Abstract]
)
AND
(
phytochemical*[Title/Abstract]
OR \plant-derived"[Title/Abstract]
OR \natural product*"[Title/Abstract]
OR polyphenol*[Title/Abstract]
OR flavonoid*[Title/Abstract]
OR alkaloid*[Title/Abstract]
OR terpen*[Title/Abstract]
OR lignan*[Title/Abstract]
OR stilben*[Title/Abstract]
)
```

The AI shall then create mechanism-specific searches.

7 Mechanism Search Modules

For each disease, construct searches for all biologically relevant domains.
Generic mechanism block:

```
(
apoptosis
OR autophagy
OR ferroptosis
OR necroptosis
OR oxidative stress
OR mitochondrial
OR inflammation
OR \NF-kB"
OR NLRP3
OR PI3K
OR AKT
OR mTOR
OR AMPK
```

```
OR MAPK
OR ERK
OR JNK
OR STAT3
OR \Wnt/beta-catenin"
OR Notch
OR Hedgehog
OR p53
OR angiogenesis
OR VEGF
OR \cancer stem cell*"
OR \DNA repair"
OR resistance
)
```

The mechanism list must be disease-specific and expanded rather than treated as universally complete.

8 Search Stratification

Every candidate should be searched in separate evidence layers.

8.1 Layer A: Identity

Search:

```
\Molecule Name"
\Chemical Name"
\CAS Number"
\PubChem CID"
\ChEBI ID"
```

Verify chemical identity using authoritative chemical databases.

8.2 Layer B: Disease

```
\Molecule Name" AND \Disease"
```

8.3 Layer C: Mechanism

```
\Molecule Name" AND
(\TARGET" OR \PATHWAY" OR \MECHANISM")
```

8.4 Layer D: Pharmacokinetics

```
\Molecule Name" AND
(pharmacokinetic* OR bioavailability OR metabolism
OR half-life OR plasma OR tissue distribution)
```

8.5 Layer E: BBB

For neurological diseases:

```
\Molecule Name" AND
(\blood-brain barrier" OR BBB OR brain penetration
OR brain/plasma OR ABCB1 OR P-gp OR ABCG2 OR BCRP)
```

8.6 Layer F: Toxicology

```
\Molecule Name" AND
(toxicity OR toxicology OR cytotoxicity
OR hepatotoxicity OR nephrotoxicity
OR cardiotoxicity OR genotoxicity)
```

8.7 Layer G: Drug Interactions

```
\Molecule Name" AND
(\drug interaction*" OR CYP OR P-gp OR ABCB1
OR ABCG2 OR hERG OR QT)
```

9 Evidence Hierarchy

Evidence shall be explicitly categorized.

Level	Definition
E0	No relevant evidence located E1
Computational prediction only E2	Biochemical/target assay evidence E3
Cell-culture evidence E4	3D/organoid/ex-vivo evidence E5
Animal/preclinical evidence E6	Human observational evidence E7
Human interventional/clinical evidence E8	Multiple independent clinical studies with consistent evidence

The AI shall never convert:
[E1 $\rightarrow E3$]
or:
[E3 $\rightarrow E7$]
without supporting evidence.
Docking is not proof of biological activity.
Network pharmacology is not proof of mechanism.
An association is not proof of causality.

10 Evidence Confidence Score

Define:

$$[\ E_i = w_L L_i + w_M M_i + w_R R_i + w_T T_i + w_C C_i]$$

where:

L_i = literature quality M_i = mechanistic experimental strength R_i = reproducibility T_i = translational rele

All normalized values satisfy:
$[\ 0 \leq x \leq 1]$
Weights must be explicitly reported and may not be silently changed during analysis.
For a strictly preclinical project, clinical evidence may be excluded from ranking rather than fabricated.

11 Source Quality Rules

Prioritize:

1. randomized clinical trials,
2. systematic reviews/meta-analyses,
3. replicated animal studies,
4. well-controlled mechanistic experiments,
5. independent cellular studies,
6. biochemical assays,
7. authoritative pharmacology/toxicology resources,
8. reputable reviews,
9. preprints,
10. computational predictions.

Reviews are discovery tools.
Primary research is required to verify specific mechanistic claims.
The AI shall locate the primary paper behind an important claim whenever possible.

12 Mandatory Candidate Record

Every molecule must be represented as a structured record:

```
Molecule_ID
Molecule_Name
Synonyms
Plant_Source
Plant_Family
Plant_Part
Chemical_Class
CAS
PubChem_CID
ChEBI
Molecular_Formula
Molecular_Weight
```

```
Disease
Evidence_Level
Primary_Targets
Secondary_Targets
Pathways
Experimentally_Demonstrated_Mechanisms
Predicted_Mechanisms
Cell_Models
Animal_Models
Human_Studies
BBB_Evidence
Brain_Penetration
Bioavailability
Half_Life
Metabolism
CYP_Interactions
P_Gp
BCRP
hERG_QT
Hepatotoxicity
Nephrotoxicity
Cardiotoxicity
Genotoxicity
Drug_Interactions
Contraindications
Adverse_Effects
TMZ_Interaction
Radiation_Interaction
Primary_References
PMID
DOI
Evidence_Confidence
Data_Gaps
```

13 Contraindication and Safety Engine

The AI shall not use the phrase "not contraindicated" merely because no contraindication was found.

Instead use:

> "No contraindication identified in the searched evidence sources; absence of evidence is not evidence of safety."

Each candidate receives:
$[\ \mathrm{S}_i = S_{\text{tox}} + S_{\text{interaction}} + S_{\text{PK}} + S_{\text{organ}} + S_{\text{cardiac}} + S_{\text{disease-specific}}]$
Each component is independently documented.

13.1 Hard Safety Gates

A candidate may be excluded from a combination hypothesis if there is strong evidence for:

- unacceptable toxicity at experimentally relevant exposure,

- severe drug interaction risk,
- clinically important QT/hERG liability,
- severe hepatotoxicity,
- severe nephrotoxicity,
- genotoxicity incompatible with the intended experiment,
- strong antagonism with required standard therapy,
- inadequate exposure where exposure is essential to the claimed mechanism,
- or inability to distinguish tumor effects from normal-cell toxicity.

These are research exclusion criteria, not clinical diagnoses.

14 Drug Interaction Matrix

For each molecule i and reference drug j calculate a qualitative interaction class:
[$I_{ij} \in$ none identified, possible, probable, demonstrated, antagonistic, synergistic, unknown]
Search:

```
\Molecule" AND \Drug"
\Molecule" AND CYP3A4
\Molecule" AND CYP2D6
\Molecule" AND CYP2C9
\Molecule" AND CYP2C19
\Molecule" AND ABCB1
\Molecule" AND ABCG2
\Molecule" AND hERG
\Molecule" AND QT
```

For disease-specific oncology workflows additionally search:

```
\Molecule" AND temozolomide
\Molecule" AND radiotherapy
\Molecule" AND bevacizumab
\Molecule" AND MGMT
\Molecule" AND DNA repair
```

15 Blood-Brain-Barrier Module

For neurological diseases, define a BBB feasibility score:
[$B_i = w_P P_i + w_T T_i + w_E E_i - w_E ff Eff_i$]
where:

P_i = passive permeability evidence T_i = transport evidence E_i = brain exposure evidence Eff_i = efflux lia

Search for:

- passive permeability,

- P-glycoprotein/ABCB1,
- BCRP/ABCG2,
- brain/plasma ratio,
- unbound brain concentration,
- transporter-mediated efflux,
- brain microdialysis,
- CSF exposure,
- metabolic stability.

Do not infer BBB penetration solely from molecular weight or lipophilicity.

16 Pharmacokinetic Feasibility

For each candidate record:
[F = bioavailability]
[$t_{1/2} = \frac{\ln 2}{k_e}$]
where k_e is the elimination rate constant.
If concentration data are available:
[AUC = $\int_0^t C(t), dt$]
For brain exposure:
[$K_{p,brain} = \frac{C_{brain}}{C_{plasma}}$]
Prefer:
[$K_{p,uu} = \frac{C_{brain,unbound}}{C_{plasma,unbound}}$]
when experimentally available.
AI-derived estimates must be labelled as predictions.

17 Tumor Selectivity

For cancer applications define:
[SI = $IC_{50,\ normal}\overline{IC_{50,\ tumor}}$]
where larger SI indicates greater experimental selectivity.
However:
[SI ¿ 1]
is not automatically sufficient.
The AI must report:

- cell type,
- assay,
- exposure duration,
- concentration,
- replicate structure,
- statistical analysis,
- and whether the result was independently reproduced.

18 Combination-Synergy Mathematics

The AI shall not assume that combining positive molecules produces a positive combination.

For two agents, use multiple synergy frameworks when data permit.

18.1 Bliss Independence

If:

[E_A = effect of A]

and:

[E_B = effect of B]

then:

[E_{AB}^{Bliss}

$E_A + E_B - E_A E_B$]

Observed combination effect:

[E_{AB}^{obs}]

Bliss deviation:

[Δ_{Bliss}

$E_{AB}^{obs} - E_{AB}^{Bliss}$]

Interpretation:

[$\Delta_{Bliss} > 0 \Rightarrow$ greater-than-expected effect]

[$\Delta_{Bliss} = 0 \Rightarrow$ Bliss independence]

[$\Delta_{Bliss} < 0 \Rightarrow$ less-than-expected effect]

The exact sign convention must be explicitly defined for the assay.

18.2 Highest Single Agent

[$E_{HSA} = \max(E_A, E_B)$]

[$\Delta_{HSA} = E_{AB}^{obs} - E_{HSA}$]

18.3 Loewe Additivity

Where appropriate, use:

[$d_A \frac{}{D_A + \frac{d_B}{D_B}}$

1]

as the additivity reference.

Combination index methods must not be mixed indiscriminately across different experimental assumptions.

18.4 Multi-Agent Extension

For n components:

[x

$(x_1, x_2, \ldots, x_n)$]

subject to:

[$x_i \geq 0$]

and:

[$\sum_{i=1}^{n} x_i = 1$]

where x_i represents the relative experimental contribution of component i in a laboratory formulation.

The optimization objective is:

[$\max_{\mathbf{x}} [E(\mathbf{x})$

$\lambda_T T(\mathbf{x})$
$\lambda_I I(\mathbf{x}) + \lambda_S Synergy(\mathbf{x})]$
subject to all hard safety constraints.

19 Multi-Objective Candidate Ranking

Define:
[$R_i = w_E E_i + w_M B_i + w_M eM_i + w_S Sel_i + w_P PK_i + w_S ySy_i$
$w_T T_i$
$w_I I_i$
$w_U U_i$]
where:

$E_i = evidencequality\ B_i \quad = BBBfeasibilitywhererelevant\ MeM_i = mechanisticcoverage\ SSel_i \quad = selectiv$

All weights must be declared before final ranking.
A high score does not mean "best treatment."
It means:
[high research priority under declared assumptions.]

20 Mechanistic Coverage Matrix

Create a binary or weighted matrix:
[M_{ij}
$\begin{cases} 1 & \text{if molecule } i \text{ experimentally affects mechanism } j \ 0 \\ \text{otherwise} \end{cases}$]
For weighted evidence:
[$0 \leq M_{ij} \leq 1$]
The combination coverage is:
[$C_j = 1 - \prod_{i=1}^{n}(1 - M_{ij})$]
This measures whether multiple components independently cover the same or complementary mechanisms.
Redundancy shall not automatically be interpreted as desirable.

21 Mechanistic Redundancy

If too many candidates target the same pathway, apply a redundancy penalty:
[$P_R = \sum_j \max(0, N_j - N_{target,j})$]
where N_j is the number of selected molecules affecting mechanism j.
The purpose is to prevent a nominally "multi-target" combination from actually being a collection of nearly identical pathway modulators.

22 100 → 20 → 10 → 5

The default workflow is:
[$100 \to 20 \to 10 \to 5$]

22.1 Stage 1: 100 Candidates

Broad discovery.

No aggressive premature filtering.

22.2 Stage 2: 20 Candidates

Apply:

- evidence verification,
- identity verification,
- mechanistic relevance,
- preliminary safety,
- PK feasibility,
- disease relevance.

22.3 Stage 3: 10 Candidates

Apply:

- independent replication,
- pathway complementarity,
- toxicity,
- interaction analysis,
- BBB feasibility where relevant,
- resistance biology,
- experimental tractability.

22.4 Stage 4: 5 Combination Hypotheses

Construct five deliberately different mechanistic combinations.

Do not simply choose the five highest-ranked molecules.

23 Combination Architecture

Each final combination should preferably contain complementary functional roles.

Example:

$[\,\text{Combination} = \text{A}_{\text{primary disease mechanism}} + B_{\text{survival/resistance}} + C_{\text{inflammation}} + D_{\text{metabolic/mitochondrial}} + E_{\text{selectivity/secondary mechanism}}]$

The number of components may be reduced if experimental evidence suggests that fewer components provide equivalent or superior performance.

Complexity is not itself evidence of superiority.

24 Laboratory Panel Design

Each final hypothesis must be tested in stages.

24.1 Panel 1: Individual Agents

Test every component independently.
Measure:

- viability,
- target engagement,
- phenotype,
- concentration-response,
- time-response,
- normal-cell toxicity.

24.2 Panel 2: Pairwise Combinations

Evaluate:
[n $\binom{}{2}$
n(n-1)$_{\overline{2]}}$
pairwise combinations.
For $n = 5$:
[5$\binom{}{2=10]}$
pairs.

24.3 Panel 3: Higher-Order Combinations

Only combinations supported by pairwise evidence proceed.

24.4 Panel 4: Disease-Relevant Models

Examples:

- primary cells,
- patient-derived cells,
- organoids,
- 3D cultures,
- co-culture models,
- microenvironment models.

24.5 Panel 5: Translational Preclinical Model

Only after cellular evidence supports progression.

25 GBM-Specific Module

For glioblastoma, the search architecture shall explicitly cover:

- EGFR,
- RTK signaling,
- RAS/RAF/MEK/ERK,
- PI3K/AKT/mTOR,
- PTEN,
- STAT3,
- NF-κB,
- Wnt/β-catenin,
- Notch,
- Hedgehog,
- p53,
- BCL-2/BAX/caspases,
- mitochondrial apoptosis,
- autophagy,
- ferroptosis,
- ROS/Nrf2,
- HIF-1α,
- VEGF/angiogenesis,
- invasion/MMPs,
- cancer stem cells,
- MGMT,
- DNA repair,
- temozolomide resistance,
- radiation response,
- tumor metabolism,
- ABCB1/P-gp,
- ABCG2/BCRP,
- BBB penetration,
- tumor-associated microenvironment.

Natural-product reviews of GBM emphasize mechanisms including apoptosis, autophagy, cell-cycle effects, metabolism, neuroinflammation, chemoresistance, angiogenesis, and BBB/bioavailability limitations; these must be treated as evidence domains rather than as proof of clinical efficacy. [3]

26 Falsification Engine

Every hypothesis must include explicit failure criteria.

A hypothesis is rejected if:

- combination activity is not reproducible,
- apparent synergy disappears under independent analysis,
- activity depends entirely on nonspecific cytotoxicity,
- normal-cell toxicity eliminates useful selectivity,
- required exposure cannot be achieved in the relevant model,
- BBB exposure is inadequate for a brain target,
- combination antagonizes standard therapy,
- mechanism cannot be reproduced after target perturbation,
- or independent experiments contradict the original finding.

The objective is not to prove the hypothesis.

The objective is to determine whether the hypothesis survives attempted falsification.

27 AI Verification Protocol

The AI must classify every important statement as:

1. **VERIFIED**
2. **SUPPORTED**
3. **PRECLINICAL**
4. **INFERRED**
5. **PREDICTED**
6. **UNKNOWN**
7. **CONTRADICTED**

The AI shall never fabricate:

- PMID,
- DOI,
- experimental result,
- concentration,
- animal dose,
- clinical dose,
- mechanism,

- plant source,
- contraindication,
- pharmacokinetic parameter.

If a citation cannot be verified:
[CitationStatus = UNKNOWN]
not:
[CitationStatus = VERIFIED]

28 Duplicate and Citation Control

Deduplicate by:

1. DOI,
2. PMID,
3. trial identifier,
4. title,
5. author/year combination.

The same study appearing in PubMed, PMC, Google Scholar, Crossref, and another database must not be counted as five independent studies.

29 Contradictory Evidence

If studies disagree, report:
[EvidenceBalance = $\sum w_k E_k^{positive} \frac{}{\sum w_k E_k^{positive} + \sum w_k E_k^{negative}}$]
This is an evidence-summary metric, not a probability of efficacy.
The AI must preserve contradictory findings rather than selectively reporting positive studies.

30 Publication Bias

The AI shall search explicitly for:

```
\Molecule" negative study
\Molecule" failed
\Molecule" toxicity
\Molecule" no effect
\Molecule" antagonism
\Molecule" null
```

Positive-only evidence is insufficient.

31 Mandatory Search Log

Every search must generate:

```
Search_ID
Database
Platform
URL
Date
Time
Query
Filters
Language
Date_Range
Result_Count
Records_Retrieved
Records_Screened
Records_Included
Search_Engine
AI_Model
Search_Version
```

The full search strings should be preserved as supplementary research data. PRISMA-S specifically recommends documenting exact search strategies and information sources so that searches can be reproduced and updated. [1]

32 Required 100-Molecule Output Grid

The final grid shall contain at minimum:

ID	Molecule	Plant	Class	Targets	Mechanism	Evidence
1	–	–	–	–	–	– 2
–	–	–	–	–	–	... 100
–	–	–	–	–	–	

A second technical table shall contain:

Molecule	BBB	PK	CYP/P-gp	Toxicity	Interaction
–	–	–	–	–	–

33 Required Final Report

The AI must output:

1. Executive summary
2. Research question
3. Search methodology
4. Complete search log

5. PRISMA-style study flow
6. 100-molecule master grid
7. Evidence hierarchy
8. Mechanistic map
9. BBB analysis where relevant
10. Pharmacokinetic analysis
11. Toxicology matrix
12. Contraindication matrix
13. Drug-interaction matrix
14. 100→20 down-selection
15. 20→10 down-selection
16. 10→5 down-selection
17. Five laboratory combination hypotheses
18. Mathematical synergy framework
19. Experimental validation sequence
20. Falsification criteria
21. Data gaps
22. Uncertainty analysis
23. Complete bibliography
24. PMID/DOI verification table

34 "Plants to Pills" Translation Layer

PHYTOFORGE-X uses the phrase:

[Plants to Pills]

as a conceptual translational pathway.

However, the actual research output is:

[Plants → Molecules → Evidence → Mechanisms → Safety → Combinations → Laboratory Formulation H
]

A "pill" shall not be represented as a human therapeutic product unless and until independent pharmaceutical development, toxicology, regulatory review, clinical trials, manufacturing controls, and appropriate approvals have occurred.

The AI shall therefore label proposed combinations:

PRECLINICAL LABORATORY FORMULATION HYPOTHESIS

and not:

TREATMENT

35 Human-Dosing Prohibition

Unless a separate, explicitly authorized clinical-pharmacology task is provided, the system shall not generate:

- human dosing schedules,
- self-treatment protocols,
- prescription instructions,
- disease-treatment claims,
- recommendations to replace approved medicines,
- instructions for administering experimental combinations.

Laboratory concentrations may be reported when they are necessary for accurately describing published experiments, but must be labelled as experimental concentrations and must not be converted into self-administration instructions.

36 Master AI Algorithm

Algorithm 1 PHYTOFORGE-X Execution Algorithm

Receive disease/target specification.
Define evidence cutoff date.
Generate disease vocabulary.
Generate plant/natural-product vocabulary.
Generate mechanism vocabulary.
Search PubMed/MEDLINE.
Search additional scholarly databases.
Record exact queries and result counts.
Deduplicate records.
Identify candidate plant molecules.
Verify chemical identity.
Retrieve primary studies.
Classify evidence level.
Extract experimentally demonstrated mechanisms.
Separate predicted mechanisms.
Extract model systems.
Extract PK/BBB information where relevant.
Extract toxicity information.
Extract CYP/transporter information.
Extract interaction information.
Search negative and contradictory evidence.
Assign evidence-confidence values.
Apply hard safety gates.
Construct mechanism matrix.
Construct evidence matrix.
Construct safety matrix.
Rank candidates.
Select top 20.
Re-evaluate independently.
Select top 10.
Construct complementary combinations.
Evaluate pairwise synergy.
Model higher-order combinations.
Select five laboratory hypotheses.
Define falsification criteria.
Define validation experiments.
Produce final report.
Perform citation audit.
Perform numerical consistency audit.
Perform hallucination audit.
Label all hypotheses as preclinical.

37 Universal AI Replication Instruction

The following instruction may be given directly to another AI system:

Execute PHYTOFORGE-X.

You are an evidence-synthesis and preclinical research-planning agent.

Given the disease or biological target supplied by the user, identify approximately 100 chemically defined plant-derived molecules with relevant scientific evidence.

Search PubMed and additional scholarly sources.

Do not rely on memory for citations.

Verify every PMID and DOI.

For every molecule determine:

1. plant source,
2. chemical class,
3. molecular identity,
4. experimentally demonstrated targets,
5. experimentally demonstrated mechanisms,
6. predicted mechanisms,
7. disease model,
8. cell model,
9. animal evidence,
10. human evidence,
11. BBB evidence where relevant,
12. pharmacokinetics,
13. metabolism,
14. CYP interactions,
15. transporter interactions,
16. toxicity,
17. contraindication evidence,
18. interactions with standard therapies,
19. negative evidence,
20. PMID,
21. DOI,
22. evidence level.

Separate demonstrated mechanisms from hypotheses.

Do not treat molecular docking as experimental validation.

Do not treat a review as equivalent to primary evidence.

Do not fabricate missing information.

Build a 100-molecule evidence matrix.

Down-select:

[100$\rightarrow$ 20 $\rightarrow$ 10 $\rightarrow$ 5]

using explicitly declared mathematical criteria.

Construct five complementary laboratory combination hypotheses.

Evaluate potential synergy using appropriate mathematical models, including Bliss, HSA, Loewe, or another justified model where appropriate.

Evaluate toxicity and interaction constraints before recommending a combination for further laboratory investigation.

For neurological diseases explicitly evaluate BBB penetration, ABCB1/P-gp, ABCG2/BCRP, brain/plasma exposure, and unbound brain exposure where available.

For cancer explicitly evaluate tumor selectivity, normal-cell toxicity, apoptosis, autophagy, ferroptosis, invasion, angiogenesis, cancer stem cells, treatment resistance, DNA repair, and interaction with standard therapy.

For metabolic disease evaluate insulin signaling, glucose transport, hepatic glucose production, beta-cell biology, inflammation, mitochondrial function, lipid metabolism, incretin biology, and relevant complications.

For every final hypothesis provide falsification criteria.

Do not provide human dosing or self-medication instructions.

Label all proposed combinations:

[**PRECLINICAL LABORATORY FORMULATION HYPOTHESIS**]

The final report must contain a complete search log, evidence table, safety matrix, interaction matrix, ranking mathematics, combination logic, references, PMID/DOI verification, uncertainty analysis, and experimental validation plan.

38 Reproducibility Requirement

A second independent AI executing the same specification should be able to reconstruct:
[Question → Search → Evidence → Selection → Combination]
without requiring undocumented human assumptions.
Every non-obvious decision must therefore have:
[Decision + Criterion + Evidence + Date + Source]
associated with it.

39 Scientific Integrity Rules

The following rules are immutable:

1. Never invent citations.
2. Never upgrade evidence levels.
3. Never equate docking with experimental validation.
4. Never equate animal efficacy with human efficacy.
5. Never equate association with causation.
6. Never suppress contradictory evidence.
7. Never claim safe" solely because toxicity was not found.
8. Never claim not contraindicated" from an incomplete search.
9. Never assume combination synergy.
10. Never convert experimental concentrations into human doses.
11. Never recommend replacing approved therapy.

12. Always preserve uncertainty.
13. Always preserve negative findings.
14. Always record the search date.
15. Always verify critical references.

40 Project Attribution

PHYTOFORGE-X™

PhytoIntelligence Evidence-to-Formulation Research and Optimization Framework
Developed for:

Scientibots PhytoIntelligence MarieLandrySpyShop.com Marie-Soleil Seshat Landry

Conceptual domain:
[AI-Assisted Natural-Product Evidence Synthesis]
Research philosophy:
[Search broadly → Verify ruthlessly → Quantify uncertainty → Attempt falsification → Test experimenta
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References

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[2] Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ.* 2021;372:n71.

[3] Mian YS, Nambiar A, Kaliaperumal C. Phytotherapy for the Treatment of Glioblastoma: A Review. *Frontiers in Surgery.* 2022. PMID: 35402495. DOI: 10.3389/fsurg.2022.844993.