

Supplementary file

Drug-drug interactions and synergy: from pharmacological models to clinical application

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Introduction

Search query 1 in MEDLINE

Synergy AND interaction AND pharmacology Filters: Review, Systematic Review

("synergies"[All Fields] OR "synergy"[All Fields]) AND ("interact"[All Fields] OR "interactant"[All Fields] OR "interactants"[All Fields] OR "interacted"[All Fields] OR "interacting"[All Fields] OR "interaction"[All Fields] OR "interactional"[All Fields] OR "interactions"[All Fields] OR "interactive"[All Fields] OR "interactively"[All Fields] OR "interactives"[All Fields] OR "interactivities"[All Fields] OR "interactivity"[All Fields] OR "interacts"[All Fields]) AND ("pharmacology"[MeSH Terms] OR "pharmacology"[All Fields] OR "pharmacologies"[All Fields] OR "pharmacology"[MeSH Subheading])) AND (review[Filter] OR systematicreview[Filter])

Translations

Synergy: "synergies"[All Fields] OR "synergy"[All Fields]

interaction: "interact"[All Fields] OR "interactant"[All Fields] OR "interactants"[All Fields] OR "interacted"[All Fields] OR "interacting"[All Fields] OR "interaction"[All Fields] OR "interactional"[All Fields] OR "interactions"[All Fields] OR "interactive"[All Fields] OR "interactively"[All Fields] OR "interactives"[All Fields] OR "interactivities"[All Fields] OR "interactivity"[All Fields] OR "interacts"[All Fields]

pharmacology: "pharmacology"[MeSH Terms] OR "pharmacology"[All Fields] OR "pharmacologies"[All Fields] OR "pharmacology"[Subheading]

Search query 2 in SCOPUS

ALL (synergy AND interaction AND pharmacology)

ALL (synergy AND interaction AND pharmacology ischaemic AND heart AND disease)

ALL (synergy AND interaction AND pharmacology AND stroke)

ALL (synergy AND interaction AND pharmacology AND chronic AND obstructive AND pulmonary AND disease)

The evolution of synergy in pharmacology: a historical perspective

Search query 3 in MEDLINE

Synergy AND ((Bliss OR MSP OR (Multiplicative Survival Principle)) OR (Loewe OR DEP OR (Dose Equivalence Principle) OR isobole) OR (Gaddum OR HSA OR (Highest Single Agent))) Filters: **Clinical Trial, Randomized Controlled Trial**
(("synergies"[All Fields] OR "synergy"[All Fields]) AND ("Bliss"[All Fields] OR "MSP"[All Fields] OR ("multiplicative"[All Fields] OR "multiplicatively"[All Fields] OR "multiplicativity"[All Fields]) AND ("mortality"[MeSH Subheading] OR "mortality"[All Fields] OR "survival"[All Fields] OR "survival"[MeSH Terms] OR "survivability"[All Fields] OR "survivable"[All Fields] OR "survivals"[All Fields] OR "survive"[All Fields] OR "survived"[All Fields] OR "survives"[All Fields] OR "surviving"[All Fields]) AND ("principle"[All Fields] OR "principle based ethics"[MeSH Terms] OR ("principle based"[All Fields] AND "ethics"[All Fields]) OR "principle based ethics"[All Fields] OR "principlism"[All Fields] OR "principled"[All Fields] OR "principles"[All Fields])) OR ("Loewe"[All Fields] OR ("1 2 dodecyloxy ethyl pyrrolidine hydrochloride"[Supplementary Concept] OR "1 2 dodecyloxy ethyl pyrrolidine hydrochloride"[All Fields] OR "dep"[All Fields]) OR ("Dose"[All Fields] AND ("equivalence"[All Fields] OR "equivalences"[All Fields] OR "equivalencies"[All Fields] OR "equivalency"[All Fields] OR "equivalent"[All Fields] OR "equivalently"[All Fields] OR "equivalents"[All Fields]) AND ("principle"[All Fields] OR "principle based ethics"[MeSH Terms] OR ("principle based"[All Fields] AND "ethics"[All Fields]) OR "principle based ethics"[All Fields] OR "principlism"[All Fields] OR "principled"[All Fields] OR "principles"[All Fields])) OR ("isobole"[All Fields] OR "isoboles"[All Fields])) OR ("gaddum"[All Fields] OR "gaddum s"[All Fields] OR "HSA"[All Fields] OR ("Highest"[All Fields] AND ("single person"[MeSH Terms] OR ("single"[All Fields] AND "person"[All Fields]) OR "single person"[All Fields] OR "single"[All Fields] OR "singles"[All Fields]) AND ("agent"[All Fields] OR "agents"[All Fields]))) AND ((clinicaltrial[Filter] OR randomizedcontrolledtrial[Filter]) AND (2014:2014[pdat]))

Translations

Synergy: "synergies"[All Fields] OR "synergy"[All Fields]

Multiplicative: "multiplicative"[All Fields] OR "multiplicatively"[All Fields] OR "multiplicativity"[All Fields]

Survival: "mortality"[Subheading] OR "mortality"[All Fields] OR "survival"[All Fields] OR "survival"[MeSH Terms] OR "survivability"[All Fields] OR "survivable"[All Fields] OR

"survivals"[All Fields] OR "survive"[All Fields] OR "survived"[All Fields] OR "survives"[All Fields] OR "surviving"[All Fields]

Principle: "principle"[All Fields] OR "principle-based ethics"[MeSH Terms] OR ("principle-based"[All Fields] AND "ethics"[All Fields]) OR "principle-based ethics"[All Fields] OR "principlism"[All Fields] OR "principled"[All Fields] OR "principles"[All Fields]

Equivalence: "equivalence"[All Fields] OR "equivalences"[All Fields] OR "equivalencies"[All Fields] OR "equivalency"[All Fields] OR "equivalent"[All Fields] OR "equivalently"[All Fields] OR "equivalents"[All Fields]

Principle: "principle"[All Fields] OR "principle-based ethics"[MeSH Terms] OR ("principle-based"[All Fields] AND "ethics"[All Fields]) OR "principle-based ethics"[All Fields] OR "principlism"[All Fields] OR "principled"[All Fields] OR "principles"[All Fields]

isobole: "isobole"[All Fields] OR "isoboles"[All Fields]

Gaddum: "gaddum"[All Fields] OR "gaddum's"[All Fields]

Single: "single person"[MeSH Terms] OR ("single"[All Fields] AND "person"[All Fields]) OR "single person"[All Fields] OR "single"[All Fields] OR "singles"[All Fields]

Agent: "agent"[All Fields] OR "agents"[All Fields]

What is synergy?

Search query 4 in MEDLINE

Search: **synergy definition pharmacology** Filters: **Review, Systematic Review** Sort by: **Most Recent**

("synergies"[All Fields] OR "synergy"[All Fields]) AND ("definite"[All Fields] OR "definitely"[All Fields] OR "definition"[All Fields] OR "definitional"[All Fields] OR "definitions"[All Fields] OR "definitive"[All Fields] OR "definitively"[All Fields]) AND ("pharmacology"[MeSH Terms] OR "pharmacology"[All Fields] OR "pharmacologies"[All Fields] OR "pharmacology"[MeSH Subheading])) AND (review[Filter] OR systematicreview[Filter])

Translations

synergy: "synergies"[All Fields] OR "synergy"[All Fields]

definition: "definite"[All Fields] OR "definitely"[All Fields] OR "definition"[All Fields] OR "definitional"[All Fields] OR "definitions"[All Fields] OR "definitive"[All Fields] OR "definitively"[All Fields]

pharmacology: "pharmacology"[MeSH Terms] OR "pharmacology"[All Fields] OR "pharmacologies"[All Fields] OR "pharmacology"[Subheading]

Models to analyze synergy

Figure S1. Outcomes provided by SCOPUS for the paper published by Chou and Talalay in 1984 concerning the Unified Theory model.



Scopus

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Advances in Enzyme Regulation • Volume 22, Issue C, Pages 27 - 55 • 1984

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PubMed ID

6382953 [↗](#)

[View less](#) [^](#)

Quantitative analysis of dose-effect relationships: the combined effects of multiple drugs or enzyme inhibitors

Chou, Ting-Chao^a; Talalay, Paul^b

[Save all to author list](#)

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6.132

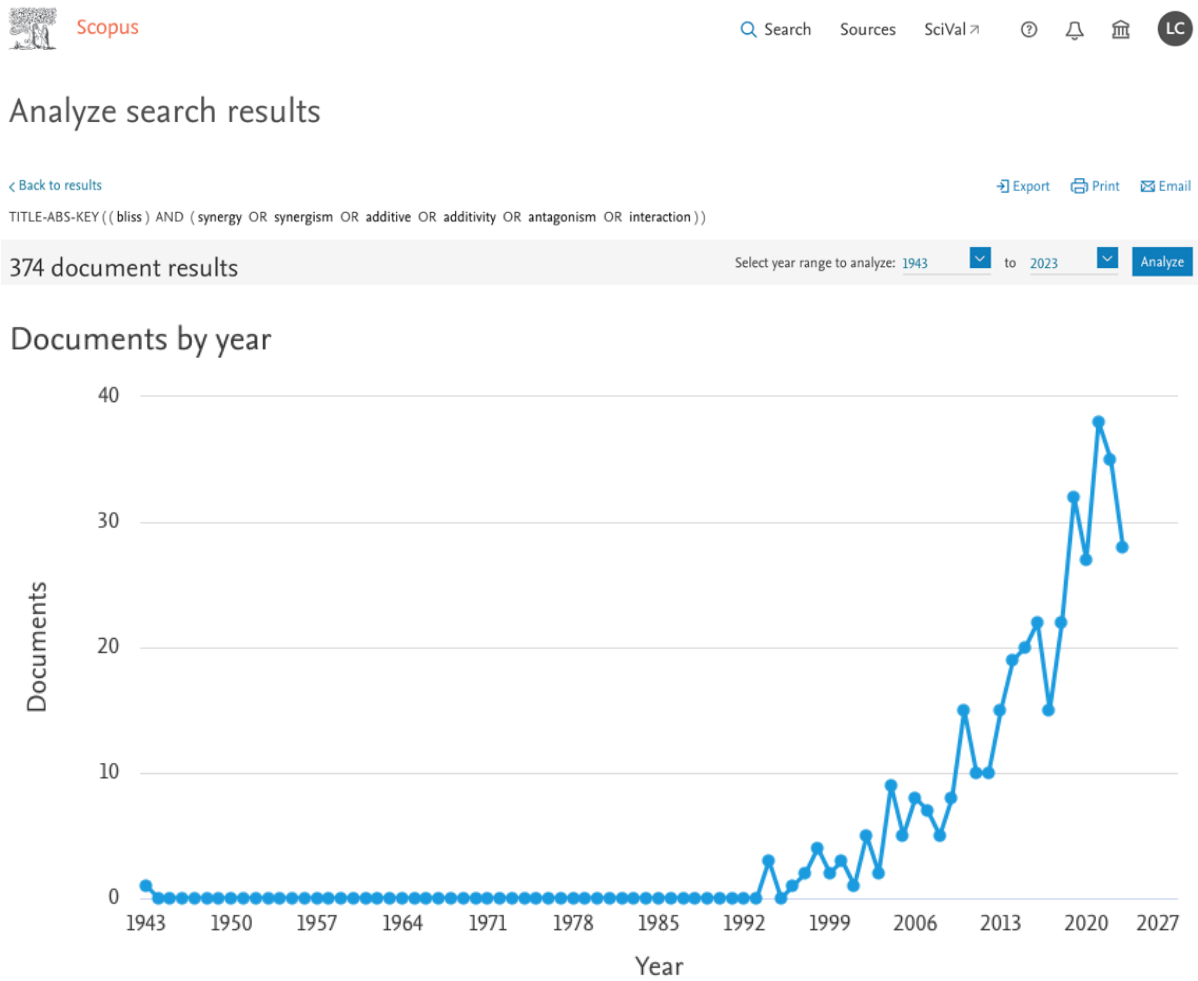
Citations in Scopus

296

Views count [?](#) [↗](#)

[View all metrics](#) [>](#)

Figure S2. Trend of citations provided by SCOPUS for the Bliss Independence model.



Synergy from bench-to-bedside

Search query 5 in MEDLINE

Search: **(antibiotic) AND (synergy) AND (combination)** Filters: **Clinical Trial, Randomized Controlled Trial** Sort by: **Most Recent**

("anti bacterial agents"[Pharmacological Action] OR "anti bacterial agents"[MeSH Terms] OR ("anti bacterial"[All Fields] AND "agents"[All Fields]) OR "anti bacterial agents"[All Fields] OR "antibiotic"[All Fields] OR "antibiotics"[All Fields] OR "antibiotic s"[All Fields] OR "antibiotical"[All Fields]) AND ("synergies"[All Fields] OR "synergy"[All Fields]) AND ("combinable"[All Fields] OR "combined"[All Fields] OR "combination"[All Fields] OR "combinational"[All Fields] OR "combinations"[All Fields] OR "combinative"[All Fields] OR "combine"[All Fields] OR "combined"[All Fields] OR "combines"[All Fields] OR "combining"[All Fields])) AND (clinicaltrial[Filter] OR randomizedcontrolledtrial[Filter])

Translations

antibiotic: "anti-bacterial agents"[Pharmacological Action] OR "anti-bacterial agents"[MeSH Terms] OR ("anti-bacterial"[All Fields] AND "agents"[All Fields]) OR "anti-bacterial agents"[All Fields] OR "antibiotic"[All Fields] OR "antibiotics"[All Fields] OR "antibiotic's"[All Fields] OR "antibiotical"[All Fields]

synergy: "synergies"[All Fields] OR "synergy"[All Fields]

combination: "combinable"[All Fields] OR "combined"[All Fields] OR "combination"[All Fields] OR "combinational"[All Fields] OR "combinations"[All Fields] OR "combinative"[All Fields] OR "combine"[All Fields] OR "combined"[All Fields] OR "combines"[All Fields] OR "combining"[All Fields]

Search query 6 in MEDLINE

Search: **(angiotensin-converting enzyme inhibitor) AND (angiotensin-II-receptor blocker) AND combination AND ((isolated artery) OR (isolated blood vessel))**
("angiotensin converting enzyme inhibitors"[Pharmacological Action] OR "angiotensin converting enzyme inhibitors"[MeSH Terms] OR ("angiotensin converting"[All Fields] AND "enzyme"[All Fields] AND "inhibitors"[All Fields]) OR "angiotensin converting enzyme inhibitors"[All Fields] OR ("angiotensin"[All Fields] AND "converting"[All Fields] AND "enzyme"[All Fields] AND "inhibitor"[All Fields]) OR "angiotensin converting enzyme inhibitor"[All Fields]) AND ("angiotensin receptor antagonists"[Pharmacological Action] OR "angiotensin receptor antagonists"[MeSH Terms] OR ("angiotensin"[All Fields] AND "receptor"[All Fields] AND "antagonists"[All Fields]) OR "angiotensin receptor antagonists"[All Fields] OR ("angiotensin"[All Fields] AND "ii"[All Fields] AND "receptor"[All Fields] AND "blocker"[All Fields]) OR "angiotensin ii receptor blocker"[All Fields]) AND ("combinable"[All Fields] OR "combined"[All Fields] OR "combination"[All Fields] OR "combinational"[All Fields] OR "combinations"[All Fields] OR "combinative"[All Fields] OR "combine"[All Fields] OR "combined"[All Fields] OR "combines"[All Fields] OR "combining"[All Fields]) AND (((("isolate"[All Fields] OR "isolate s"[All Fields] OR "isolated"[All Fields] OR "isolates"[All Fields] OR "isolating"[All Fields] OR "isolation and purification"[MeSH Subheading] OR ("isolation"[All Fields] AND "purification"[All Fields]) OR "isolation and purification"[All Fields] OR "isolation"[All Fields] OR "isolations"[All Fields]) AND ("arterialization"[All Fields] OR "arterializations"[All Fields] OR "arterialize"[All Fields] OR "arterialized"[All Fields] OR "arterializing"[All Fields] OR "arterially"[All Fields] OR "arterials"[All Fields] OR "arterie"[All Fields] OR "arteries"[MeSH Terms] OR "arteries"[All Fields] OR "arterial"[All Fields] OR "arteris"[All Fields] OR "artery"[All Fields] OR "arterious"[All Fields] OR "artery s"[All Fields] OR "arterys"[All Fields])) OR (("isolate"[All Fields] OR "isolate s"[All Fields] OR "isolated"[All Fields] OR "isolates"[All Fields] OR "isolating"[All Fields] OR "isolation and purification"[MeSH Subheading] OR ("isolation"[All Fields] AND "purification"[All Fields]) OR "isolation and purification"[All Fields] OR "isolation"[All Fields] OR "isolations"[All Fields]) AND ("blood vessels"[MeSH Terms] OR ("blood"[All Fields] AND "vessels"[All Fields]) OR "blood vessels"[All Fields] OR ("blood"[All Fields] AND "vessel"[All Fields]) OR "blood vessel"[All Fields]))))

Translations

angiotensin-converting enzyme inhibitor: "angiotensin-converting enzyme inhibitors"[Pharmacological Action] OR "angiotensin-converting enzyme inhibitors"[MeSH

Terms] OR ("angiotensin-converting"[All Fields] AND "enzyme"[All Fields] AND "inhibitors"[All Fields]) OR "angiotensin-converting enzyme inhibitors"[All Fields] OR ("angiotensin"[All Fields] AND "converting"[All Fields] AND "enzyme"[All Fields] AND "inhibitor"[All Fields]) OR "angiotensin converting enzyme inhibitor"[All Fields]

angiotensin-II-receptor blocker: "angiotensin receptor antagonists"[Pharmacological Action] OR "angiotensin receptor antagonists"[MeSH Terms] OR ("angiotensin"[All Fields] AND "receptor"[All Fields] AND "antagonists"[All Fields]) OR "angiotensin receptor antagonists"[All Fields] OR ("angiotensin"[All Fields] AND "ii"[All Fields] AND "receptor"[All Fields] AND "blocker"[All Fields]) OR "angiotensin ii receptor blocker"[All Fields]

combination: "combinable"[All Fields] OR "combined"[All Fields] OR "combination"[All Fields] OR "combinational"[All Fields] OR "combinations"[All Fields] OR "combinative"[All Fields] OR "combine"[All Fields] OR "combined"[All Fields] OR "combines"[All Fields] OR "combining"[All Fields]

isolated: "isolate"[All Fields] OR "isolate's"[All Fields] OR "isolated"[All Fields] OR "isolates"[All Fields] OR "isolating"[All Fields] OR "isolation and purification"[Subheading] OR ("isolation"[All Fields] AND "purification"[All Fields]) OR "isolation and purification"[All Fields] OR "isolation"[All Fields] OR "isolations"[All Fields]

artery: "arterialization"[All Fields] OR "arterializations"[All Fields] OR "arterialize"[All Fields] OR "arterialized"[All Fields] OR "arterializing"[All Fields] OR "arterially"[All Fields] OR "arterials"[All Fields] OR "arterie"[All Fields] OR "arteries"[MeSH Terms] OR "arteries"[All Fields] OR "arterial"[All Fields] OR "arteris"[All Fields] OR "artery"[All Fields] OR "arterious"[All Fields] OR "artery's"[All Fields] OR "arterys"[All Fields]

isolated: "isolate"[All Fields] OR "isolate's"[All Fields] OR "isolated"[All Fields] OR "isolates"[All Fields] OR "isolating"[All Fields] OR "isolation and purification"[Subheading] OR ("isolation"[All Fields] AND "purification"[All Fields]) OR "isolation and purification"[All Fields] OR "isolation"[All Fields] OR "isolations"[All Fields]

blood vessel: "blood vessels"[MeSH Terms] OR ("blood"[All Fields] AND "vessels"[All Fields]) OR "blood vessels"[All Fields] OR ("blood"[All Fields] AND "vessel"[All Fields]) OR "blood vessel"[All Fields]

Search query 7 in MEDLINE

Search: **drug combination additive effect**[title] Filters: **Clinical Trial, Randomized Controlled Trial**

("drug combinations"[MeSH Terms] OR ("drug"[All Fields] AND "combinations"[All Fields]) OR "drug combinations"[All Fields] OR ("drug"[All Fields] AND "combination"[All Fields]) OR "drug combination"[All Fields]) AND "additive effect"[Title]) AND (clinicaltrial[Filter] OR randomizedcontrolledtrial[Filter])

Translations

drug combination: "drug combinations"[MeSH Terms] OR ("drug"[All Fields] AND "combinations"[All Fields]) OR "drug combinations"[All Fields] OR ("drug"[All Fields] AND "combination"[All Fields]) OR "drug combination"[All Fields]

Concentrations (doses), site of action, and timing: the trilogy for optimizing synergy

Search query 8 in MEDLINE

Search: (bi-functional[title] OR bifunctional[title] OR multi-functional[title] OR multifunctional[title]) AND drugs[title] Filters: Review Sort by: Most Recent
(("bi-functional"[Title] OR "bifunctional"[Title] OR "multi-functional"[Title] OR "multifunctional"[Title]) AND "drugs"[Title]) AND (review[Filter])