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Review

Synergy research: Approaching a new generation of phytopharmaceuticals

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ABSTRACT

The longstanding, successful use of herbal drug combinations in traditional medicine demands that we find a rationale for their comparative pharmacological and therapeutic superiority to isolated single constituents. The synergistic efficacy of these combinations can be evaluated and verified by Berenbaum's isobole method, followed by clinical studies performed in comparison with synthetic standard drugs. There are many examples of mono- and multi-extract combinations used presently, which exhibit synergistic efficiency based on multi-target mechanisms of action. Among the natural products, gallocatechins of green tea and curcuminoids of ginger are the presently favoured polyphenols for a possible future use in co-medication with antibiotics and standard anticancer drugs. The main targets were found to be COX 1 + 2, NF-κB, and membrane glycoproteins that belong to the ATP-binding cassette (ABC) transporter family.

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1. Introduction

Synergy assessment has become a key area in phytomedicine research in recent years. It is the aim of this research to find a scientific rationale for the centuries-old, often-observed therapeutic superiority of many multidrug combinations in traditional medicine over single constituents. Chemotherapy has also seen a gradual transition from the long and passionately advocated mono-substance therapy toward a multidrug therapy. It is becoming increasingly obvious through observation that many diseases possess a multi-causal etiology and a complex pathophysiology, which can be treated more effectively with well-chosen drug combinations than with a single drug. Today multidrug therapy is practiced worldwide in the

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treatment of AIDS and other infectious diseases, hypertension, numerous types of cancer and rheumatic diseases.

2. Pharmacological approach

How can we prove the existence of synergistic efficacy of a given mixture of drugs? Among the many methods proposed, the "isobole method" of Berenbaum [1] seems to be one of the most practicable in terms of experimental design, and also the most effective in demonstrating synergy.

Fig. 1 shows an example for the verification of a synergistic effect resulting from the combination of the two known natural products, ginkgolides A and B, of *Ginkgo biloba*, using the PAF-induced in vitro thrombocyte aggregation inhibition test [2,3]. As shown in the chart, the interaction index is <1 and therefore corresponds to the isobole that is concavely curved towards the zero point. In this case, we have a real synergistic or potentiated (over-additive) effect which can be expressed as $E\ (d_a, d_b) > E\ (d_a) + E\ (d_b)$, meaning that the effects of the two drugs A and B applied together as a mixture are larger than what would be expected from the sum of the two separate effects [4].

3. What are the possible mechanisms underlying the synergy effects?

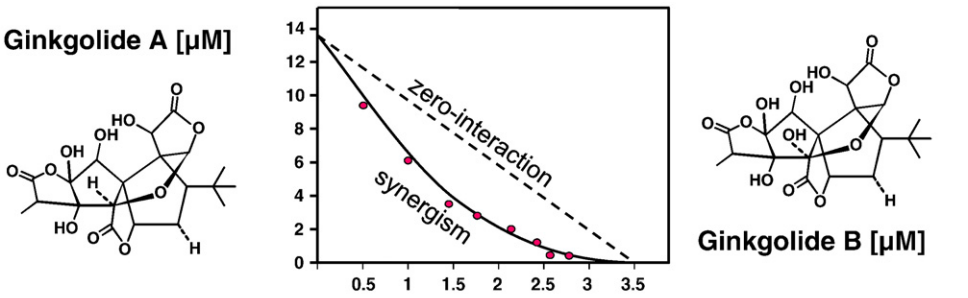
Based on results from the latest classical pharmacological and clinical investigations, the following four mechanisms can be described:

1. Synergistic multi-target effects, in which the single constituents of a mono- or multi-extract combination affect not only one single target, but several targets such as enzymes, substrates, metabolites, receptors, ion channels, transport proteins, DNA/RNA, ribosomes or monoclonal or antibodies [5].
2. Pharmacokinetic or physicochemical effects based on improved solubility, or physico-chemical effects based on improved solubility of constituents of an extract by one or several other components of the same extract [6,7].
3. Antagonization of resistance mechanisms of pathogenic microorganisms (bacteria, fungi) or tumor cells by natural products (e.g., polyphenols such as epigallocatechingallate or curcuminoids) that are applied together with antibiotics [8] or cancer drugs. In current cancer therapy, this multi-drug concept has been designated as "biomodulatory-metronomic chemotherapy" [5].
4. The respective elimination or neutralisation of toxic or adversely acting substances by one agent that has been added to an extract. This is a frequent procedure in traditional Chinese medicine, aimed at improving the efficacy of an herbal drug preparation and resulting in "pre-treated drugs" [9].

Table 1
Examples of botanical mono-extracts which exhibit synergistic effects according to the definition of Berenbaum [1] (selected examples from [4]).

Herbal drug	Investigated mono-extract mixtures and single constituents
Ginkgo biloba	Ginkgolide mixtures, Ginkgo extract
Piper methysticum	Kava lactones/mixtures of Kava lactones and extract fractions
Glycyrrhiza glabra	Liquorice extract potentiates other substances and acts as detoxifier
Cannabis sativa	Cannabis extract/THC
Valeriana officinalis	Valeriana extract, individual constituents
Zingiber officinalis	Zingiber extract/mixture of volatile terpenoids and mixtures

Table 1 lists examples of mono-extracts which, according to the definition of Berenbaum [1], exhibit synergistic effects. This postulation is based on detailed pharmacological and molecular-biological investigations of subfractions and isolated compounds of the single extracts. Which of the four mechanisms described earlier are involved in these effects



GA : GB	IC50 [µg/ml]	Ginkgolide A [µM]	Ginkgolide B [µM]
3 : 1	2.40	4.41	1.42
2 : 1	2.20	3.60	1.72
1 : 1	1.80	2.21	2.12
1 : 2	1.55	1.27	2.43
1 : 3	1.40	0.88	2.57
1 : 10	1.30	0.29	2.79

Fig. 1. Isobole curve for 50% inhibition of a combination of ginkgolides A and B; IC_{50} values (µg/ml) of PAF-induced in vitro thrombocyte aggregation are shown for various dose combinations [2,3].