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Short communication

# Synergy: Easier to say than to prove

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According to Wikipedia synergy is "Two or more agents working together to produce a result not obtainable by any of the agents independently." Mathematically it means the impossible equation $1+1>2$, biologically it means life. Living organisms are based on all sorts of synergy, for example enabling all the chemical reactions of metabolism. In the discussion on medicinal plants often synergy is used as an argument to explain activity, and even to argue that medicinal plants are superior to single pure compounds [1–3]. Also in the resistance of plants against pest and diseases synergy might play a role (e.g. [4]). For example, plants are resistant against most microorganisms, but despite extensive studies by many groups worldwide, no one has been able to develop a novel antibiotic from a plant. Compounds with antimicrobial activity have been found but none of these have an activity at a level that seems sufficient for a promising antibiotic lead compound. After almost 100 years we are losing our battle against pathogenic microorganisms as they have developed resistance against a single pure compound like penicillin. Apparently plants are more clever than we, they seem to use a combination of traits to resist against microbes.

But how much real evidence is there for synergy? First of all there is the question what is synergy really, as the weak part of the mentioned definition is in the word result. For example, in case of medicines is the synergy of two compounds causing a lower blood pressure or less risk of cardiovascular diseases, i.e. a specific or a less specific activity. In terms of pharmacological activity the synergy could be on the level of the pharmacokinetics and/or pharmacodynamics.

To proof synergy between two or more components one thus need to define a measurable endpoint. For a certain well defined biological activity isobolograms can be used [5–9]. They show a plot in which one can see that the same activity can be obtained at a lower dose of an active compound, by mixing it with another compound, i.e. the activity is higher than the sum of the activities of these two compounds separately. Many studies on synergy apply this method to proof synergy of two compounds, however, this requires that one knows the active compound(s) of a medicinal plant. If these are not known it becomes difficult. With possibly tens of thousands different compounds present in a single plant the number of possible combinations is almost infinite, moreover the synergy can also be of an active compound and an inactive compound, or even a combination of two or more non-active compounds might show an activity.

The only solution seems a systems biology approach [10–12]. By measuring the metabolic profile of different extracts of a medicinal plant or fractions thereof and combining that information with the results of the bioassays of these samples, one may identify the signals that correlate with activity. These signals may be due to one or more compounds. After identification of these compounds, e.g. after isolation via metabolomics guided fractionation, one can test these compounds for synergy. Some recent work in this field by Choi and co-workers [13] reported the potentiating effect of isoflavonoids on the activity of antibiotics.

If synergy would play an important role in medicinal plants, the synergistic effect is on the system as a whole, and thus synergy may have many forms, also depending on the parameter that is the measure for activity, e.g. is it the cure of a disease or the effect on a single target to name the extremes. That means for studies on synergism one should use preferably in-vivo bioassays, and if possible even apply this approach in clinical trials, as besides synergy also prodrugs may be present in medicinal plants.

Obviously such an approach is totally different from the currently accepted approaches to drug development which are based on the single target single compound paradigm. The fact that HIV now can be kept under control by using a combination of several drugs, are a first sign that a paradigm shift is on its way, bringing natural products and medicinal plants again to the forefront of drug discovery.

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There is a lot to be learned from Nature and our Ancestors.

## Conflict of interest

No conflict of interest.

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