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Multitarget therapy – The future of treatment for more than just functional dyspepsia

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Abstract

Since many years the concept of classical phytotherapy using herbal drug combinations with superior efficacy and lesser side effects in comparison with single isolated constituents of plant extracts has been repeatedly assessed clinically as well as pharmacologically. For this as multitarget therapy defined treatment lot of examples are presented. The exact mechanisms of action underlying these synergy effects is unknown. It could be explained by a multitarget action of compounds on a molecular level or partly by an improved resorption rate and a change of pharmacokinetic. Progress in the field of drug synergy research may lend with standardized plant extracts a new legitimacy and may open the chance to use extract combinations for the treatment of diseases which previously have been reserved for chemotherapeutics only.

Keywords: Multitarget therapy; Synergy effects; Molecular pharmacology; Clinical evidences

Some pharmacological and clinical evidences for the Multitarget Therapy concept

Multitarget Therapy is a new therapy concept which tries to treat diseases with a multidrug combination in a more causally directed manner.

Physicians practizing phytotherapy recognized very early that a greater efficacy can be achieved with the application of a combination of plant extracts than with a (usually high dosed) monodrug. They noticed that this therapy concept at the same time has the advantage of reducing or eliminating side-effects due to the lower doses of the single compounds or drug components within the extract mixtures. For the same reason the current phytotherapy of the West, similar to the traditonal medicine of China, India, Africa and South-America, uses phytopreparations which are composed of several herbal drug extracts. The idea underlying this concept of drug medication derives from the assumption that a complex multifactorial pathophysiology (multi-causality) can be managed more effectively through the use of a correspondingly composed multidrug mixture than with a single drug. This concept aligns well with the experimental results of the modern molecularbiology, according to which optimal effects are achievable only with a medication directed simultaneously against the various causes of diseases and the already existing cellular damages caused by the illness.

In this context, it is not very surprising that also in chemotherapy, which for a long time advocated mono-drug therapy only, a gradual trend can be seen away from the monosubstance dogma toward multidrug application. Today, a series of illnesses such as cancer, AIDS or hypertension are treated successfully with synthetic drug combinations containing 3–5 single

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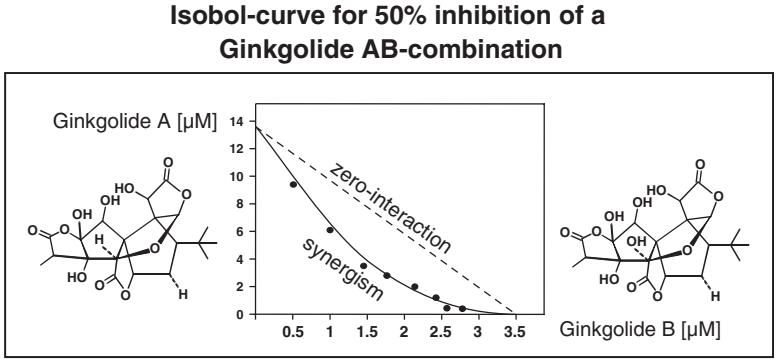
(a)



(b)

IC_{50} - values for various dose-combinations of PAF-induced thrombocyte aggregation

GA : GB	IC_{50} [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. (a) Isobol-curve for 50% inhibition of a Ginkgolide AB-combination; (b) IC^{50} – values for various dose-combinations of PAF-induced thrombocyte aggregation.

individual components. Meanwhile the advantages and superiorities of the drug combinations over single drug components have been assessed for chemotherapeutics and phytopreparations in several controlled clinical trials.

The task for phytotherapy is to prove the advantages of the multidrug- and multitarget therapy in pharmacological and clinical studies, as evidenced in this supplement issue for the multiextract preparation Iberogast® (see contributions in this supplementary Phytomedicine issue).

For many years, the therapeutic superiority of a plant drug combination over a mono extract had only the support of practical experiences. The first approach toward rationalizing this multidrug therapeutic concept was made by Berenbaum (1989). He described the results of synergy effects using two mathematical equations in which the effect of a drug combination is compared with that of its components. According to the first equation, 'a total effect of a combination is greater than expected from the sum of the effects of the single components' i.e. $E\ (d_a, d_b) > E\ (d_a) + E\ (d_b)$. The second equation states that 'synergy is deemed present if the effect of a combination is greater than that of each of the individual agents' (i.e. $E\ (d_a, d_b) > E\ (d_a)$ and $E\ (d_a, d_b) > E\ (d_b)$. ($E =$ observed effect and d_a and d_b are the doses of agents a and b) (Williamson, 2001).

How can the suggested synergy effect of a mixture containing two substances determined? The method of choice is the isobole method, which is independent of the mechanism of action. An isobol is an "iso-effect" curve, in which a combination of constituents (d_a, d_b) is represented on a graph, the axes of which are the dose axes of the single agents (d_a and d_b). Our pharmacological in vitro study of a combination of Ginkgolide A and B (Fig. 1) is a relevant example (Steinke and Wagner, 2006). In the pharmacological in vitro test, the inhibition of the PAF-induced thrombocyte aggregation was measured using various mixtures of Ginkgolide A and B. As shown in the graph, it is evident that the Ginkgolide mixture possesses an overadditive or potentiated effect and not an additive effect as expected for a 0-interaction. This Isobol method is applicable for a mixture of pure substances and only in some ideal cases also for two plant extracts.

Another example for the existence of synergy effects has been published by Baker et al. (2000). The graph in Fig. 2 shows the antispastic activity of a standardized Cannabis-extract and its major constitutent Δ^9 Tetrahydrocannabinol at an equivalent dose, as measured in an immunogenic model of multiple sclerosis.

This synergistic effect, demonstrated with the Cannabis extract, is probably due to the presence of Cannabidiol in the extract, which elevates the level of THC in the brain and at the same time attenuates the undesired anxiolytic effect of THC (Zuardi et al., 1982; Williamson and Evans, 2000).

Table 1 lists some plants extracts, which have been compared in pharmaclogical investigations with the major bioactive compounds or extract fractions thereof. In all cases, the pharmacological superiority of the extracts over the isolated compounds could be demonstrated (Table 1). In a pharmacological experiment performed recently by Capasso and Sorrentino, (2005)

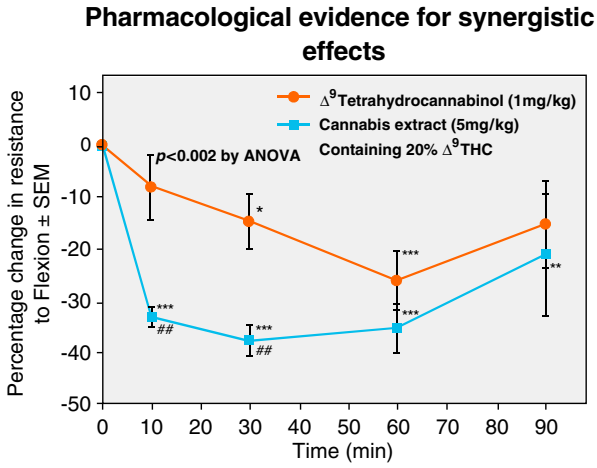


Fig. 2. Pharmacological evidence for synergistic effects. Cannabis extract is a better antispastic agent in mice than tetrahydrocannabinol (THC) at an equivalent dose. Baker, et al. (2000); Williamson, E.M. (2001).

Table 1. In vitro and in vivo pharmacological evidences for synergy effects (according to Williamson, Phytomedicine 8(5):401–409 (2001)

Ginkgo biloba:	Ginkgolide mixtures/Ginkgo extract	Chung et al. (1987)
Piper methysticum:	Kava lactones/mixtures of Kava lactones and extract fractions	Singh and Blumenthal (1997)
Glycyrrhiza glabra:	Licorice extract potentiates other substances and acts as detoxifier	Cantelli-Forti et al. (1994), Kimura et al. (1992), Miaorong and Jing (1996)
Cannabis sativa:	Cannabis extract/THC	Zuardi et al. (1982), Baker et al. (2000)
Valeriana offic.:	Valeriana extract/individual constituents	Hölzl (1997)
Zingiber offic.:	Zingiber extract/mixture of volatile terpenoids and mixtures	Beckstrom-Sternberg and Duke (1994)
Kava-kava + *Passiflora incarn.*		Capasso and Sorrentino (2005)

using a standardized extract combination of *Kava-Kava* and *Passiflora* the superiority of the combination over the single extracts in an sedative and hypnotic test model was shown. (Fig. 3). The graph shows the grade of reduction of the amphetamine-induced hypermotility produced by the single extracts of *Passiflora* and *Kava-Kava* and by the extract combination as measured against the control. The quantitatively assessed effect showed an approximately 50% higher efficacy of the extract combination in comparison with the single extracts. A similar result could be achieved in a second experiment using the barbiturate-sleeping model. The sleeping prolongation time was also approximately 50% longer with the extract combination than with the single extracts.

What could be the possible mechanisms of action underlying these synergy effects?

- One explanation could be that some by-products in the extract, e.g. saponins or tannins which themselves do not possess any specific pharmacological effect, increase the solubility or resorption rate of one of the major constituents and thereby enhance its bioavailability. Such an interaction has been described for procyanidins of *Hypericum* extract, which improved the water solubility of hypericin and thereby increased its pharmacological activity in the forced swim test of *Porsolt* (Butterweck et al., 2004). (Fig. 5)
- Another possible explanation could be that certain constituents exhibit antagonistic effects against some toxic compounds (detoxifying effect) and thereby improve the total pharmacological profile of the plant extract.
- One of the aforementioned reasons may explain the amplificatin of an effect by a factor 2 or 3 but not by a factor 10 or more. Here the pharmacological polyvalence of many plant constituents and interactions on a molecular level come into action.
- Possible interactions of the single constituents with special enzymes, mediators in the signal transduction pathway, or on genes may be taken into consideration. All these mechanisms together could explain the beneficial results of a multitarget therapy.

From the clinical side, one might object that the transferability of pharmacologically discovered and verified synergistic effects to a therapeutic use in humans is uncertain and without any evidence (Schulz, 2005). This argument cannot be contradicted. Therefore, all synergistic effects found in experiments – be they in vitro or animal studies – must be scrutinized in clinical studies.

The best evidence is provided by controlled clinical studies in parallel with synthetic drugs at the same indication. In the last 10 years, about 400 clinical, double-blind, placebo-controlled studies have been carried out with standardized plant extracts, among them about 10% against established synthetic drugs.

In Table 2 are shown some of the most important registered mono-extract preparations and two multidrug preparations, along with their corresponding synthetic competitors for given indications. The results have surprised the clinical medical establishment, because in all cases the plant extract preparations at the same indications were found to be fully therapeutically equivalent to the synthetics with the advantages of only few or no side effects.

This holds true also for the multidrug preparation Iberogast®, the subject of this supplementary Phytomedicine issue. Fig. 4 shows the pharmacological profile of each single extract component of the 9 extracts containing phytomedicine. Each extract component contributes

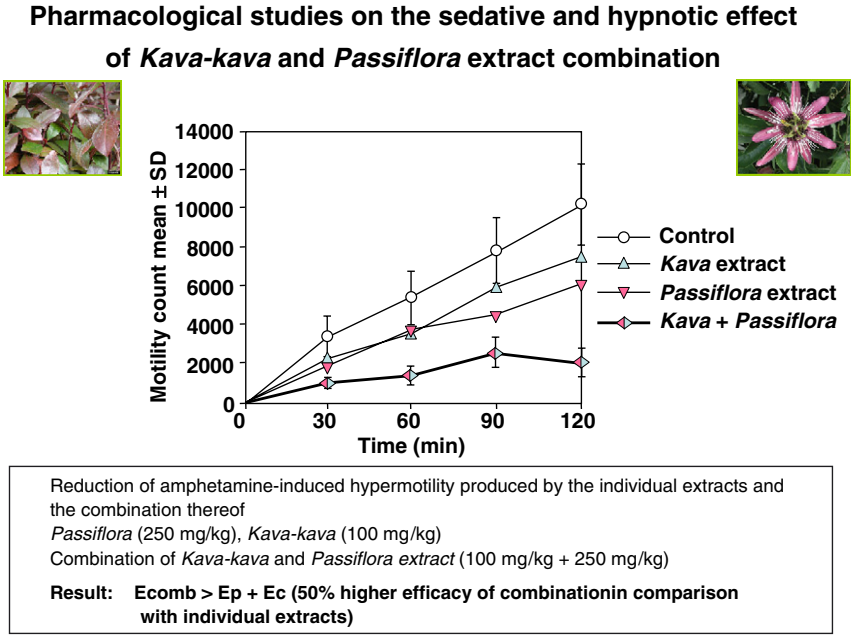


Fig. 3. Pharmacological studies on the sedative and hypnotic effect of *Kava-kava* and *Passiflora* extract combination (Capasso, A., Sorrentino, L., 2005. Phytomedicine 12, 39–45. Reduction of amphetamine-induced hypermotility produced by the individual extracts and the combination, thereof *Passiflora* (250 mg/kg), *Kava-kava* (100 mg/kg), combination of *Kava-kava* and *Passiflora extract* (100 mg/kg + 250 mg/kg). *Result*: $E_{comb} > E_p + E_c$ (50% higher efficacy of combination in comparison with individual extracts.

Table 2. Therapeutic equivalence of stand. plant extracts with synthetic drugs, evidenced by comparative placebo controlled clinical studies

Herbal extract	Chem. synth. drug	Indication
Crataegus (Hawthorn)	Captopril	Heart insufficiency, I + II NYHA
Hypericum (St. John's Wort)	Imipramine® Amitriptyline®	Moderate and moderately severedepression
Sabal (Saw palmetto)	Proscar® (Finasteride)	Benign prostate hyperplasia I + II
Hedera helix (Ivy)	Ambroxol®	Chronic bronchitis
Boswellia (Incense)	Sulfasalazin	Morbus Crohn
Iberogast® (9 extracts containing phytopharmaceutic)	Metoclopramid/ Cisaprid	Functional dyspepsia, irritable colon
Sinupret® (9 extracts containing phytopharmaceutic)	Ambroxol®	Sinusitis

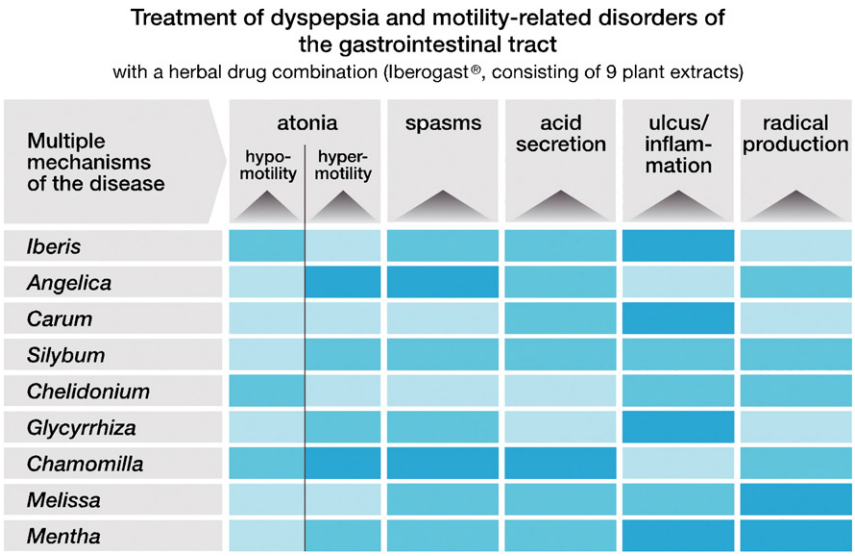


Fig. 4. Treatment of dyspepsia and motility-related disorders of the gastrointestinal tract with a herbal drug combination (Iberogast®, consisting of 9 plant extracts). —none, —moderate, —strong effects.

to one, two or three effects of the overall pharmacological profile of this multidrug preparation.

In two examples, the monoextracts of *Salix alba* (willow bark) and *Hypericum perforatum* (St. John Wort), the accomplishment of synergy effects within the extracts should be explained. (Table 3). The *Hypericum* extract contains several classes of compounds, of which hyperforin is assumed to be the dominant bioactive compound possessing antidepressant activity. The accompanying compounds are the hypericins, flavonoids, proanthocyanidins, xanthons and cinnamoyl derivatives.

The pharmacologists therefore performed many experiments to elucidate the mechanisms of action and to clarify whether hyperforin alone is responsible for the antidepressive activity or some of the other compounds contribute synergistically to the overall antidepressive indication. In vitro and in vivo investigations have shown that hyperforin is indeed a broad-spectrum uptake inhibitor for the transmitters serotonine, noradrenaline, dopamine and GABA (Müller and Holoubek, 2003). The forced swim test and pharmakokinetic studies revealed, however, that the procyanidin, B2 or hyperoside behave as potent adjuvants to assist in the reuptake inhibition of the transmitters when added to hyperforin-free, but hypericin containing St. John's Wort extract. Both phenolic compounds increased the oral bioavailability of hypericin by about 58% (B2) and 34% (hyperoside), respectively (Reichling et al., 2003; Butterweck et al., 2003; Schulz, 2003) (Fig. 5).

The total extract represents the active drug and the full antidepressent effect can be explained only through the synergy of all major compounds. Hyperforin and hypericin alone are insufficient to explain the clinically proven full antidepressent effect.

Table 3. Clinical evidences of synergy effects (according to Williamson, 2001)

- *Salix alba* (Schmidt et al., 2001)
- *Hypericum perf.* (Schulz et al., 2003)
- *Valeriana off.* + *Humulus lupulus* (Hindmarch, 1975)
- *Valeriana*+*Kava-kava* (Wheatley, 2001)
- *Urtica dioica*+*Pygeum africanum* (Hartmann et al., 1996)
- *Ginseng* + *Ginkgo* (Scholey and Kennedy, 2002)

A similar conclusion can be drawn from pharmacokinetic studies of the "active principles" of willow bark. A willow bark extract containing salicylalcohol derivatives standardized on a salicin equivalent of 17.6% was administered to patients with osteoarthritis in an extract concentration equivalent to 240 mg salicin/day. Salicin and derivatives have to be converted in the liver into salicylic acid before they can reveal their antiphlogistic and analgesic effects. The application of this amount of willow bark extract was sufficient. At a bioavailability of 100% 240 mg salicin equivalent would produce no more than 115 mg salicylic acid. In the serum, however only 1.4 mg/l were measured. For comparison, after application of 500 mg acetylsalicylic acid 35–50 mg/l can be found, the amount necessary for therapeutic equivalence with willow bark. This comparative study indicates that additional compounds, e.g. other salicylalcohol compounds, flavonoids or catechins in the extract, must participate synergistically on the clinical efficacy (Schmidt et al., 2001).

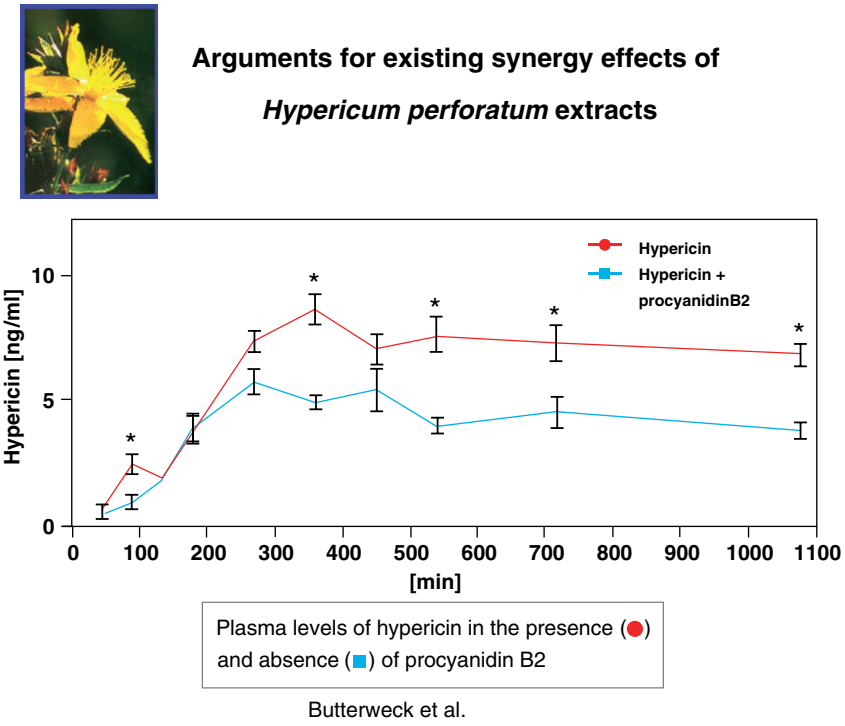


Fig. 5. Arguments for existing synergy effects of *Hypericum perforatum* extracts The accompanying procyanidin B2 and hyperoside of the hypericum extract increase the water solubility and oral bioavailability of hypericin by 58%/34% as evidenced by the *forced swim test* (Porsolt test). Plasma levels of hypericin in the presence (●) and absence (■) of procyanidin B2. Butterweck, et al., 2003. Planta Med. 69, 189–192.

Additional existing synergy effects have been described also for a combination of two plant extracts as listed in Table 3.

One must concede realistically that the methods of synergy research described here, for the meantime, will be used primerily for registered phytopreparations of the market, such as the Iberogast® presented in this supplement issue of Phytomedicine. This is due to the hurdle of our drug regulations, which prescribes that each new or altered composition of a phytopreparation is classified as novel and must be reinvestigated in expensive toxicological and clinical tests.

The example of *Hypericum,* however, shows that an effective research alliance between chemists, pharmacologists, molecular biologists and clinicians is worthwhile, if the necessary financing can be secured.

Synergy research holds the future and is part of a trend. The current impetus in medicinal fields is to develop therapy approaches with which diseases such as cancer or infections can be treated at a more causal level. The following two examples may explain the aim of this new strategy and how such new drug combinations could be developed. In a future tumor therapy, the direct destruction of tumor cells using cytostatic drugs will no longer be the primary goal. Rather, the activation or suppression of mechanisms that directly or indirectly inhibit tumor growth will take center stage. This might include a combination therapy with medicines that stimulate apoptosis, inhibit angiogenesis, activiate the immune system against tumors, inhibit oncogene expression, or stimulate repair-mechanisms in damaged cell. A well-coordinated combination could succeed in producing a medicinal cocktail that would activate such mechanisms, fighting the tumor via synergistic effects without damaging healthy tissue. (Fig. 6). A second example could be a new treatment for Hepatitis B and C. The existing methods of treatment with Interferon and/or Ribaverin have response rates of 40–50% only and entail considerable side-effects. In this case, combinations of bioactive compounds that do not have the direct destruction of the virus as their central target are required. Rather, they would again activate the mechanisms that affect the body‘s own resistance mechanisms against the virus, stimulating the immune system, blocking the adhesion of viruses to the liver cells and inhibiting the inflammatory and fibrotic processes excited by the virus. The aim of development would also be a medicinal cocktail that weakens the virulence of the hepatitis virus without major side-effects, so that the viruses could be fully eliminated by the immune system. This vision could become reality, if the new concepts in therapy receive support through molecular-pharmacological research.

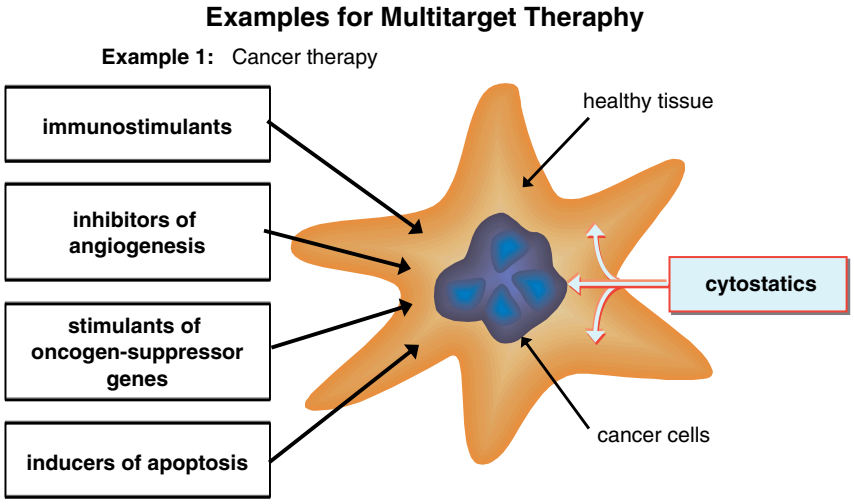


Fig. 6. Examples for multitarget therapy.

These two examples of possible new developments in medicinal preparations show that research on the complexity of illness events can be advanced with the help of molecular biological assays and research on synergistic drugs effects. Phytomedicinal research should orient itself more firmly in this new direction, as it seems clear that through progress in multi-target therapies, phytotherapy itself will gain more legitimacy and new phytodrug combinations for diseases which up to now have been treated only through chemotherapy.

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