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REVIEW PAPER

Combination screening of synthetic drugs and plant derived natural products—Potential and challenges for drug development

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Summary Plants are a precious source for medicine and drug development. An estimated one third of our present medicines are derived from natural sources – either directly isolated, synthesized or semi-synthesized by structural modification of their natural compounds. Well known examples are colchicine, morphine, semi-synthetic aspirin, taxol or penicillin. However, drug development from natural sources as well as by synthesis is presently facing a set back. Most new drugs fail in the step from the preclinic to the clinic; equally a loss of activity is observed during the bioactivity screening of plant extracts for the identification of active single constituents. The source material has often a superior activity over the isolated single constituents which give reasons to doubt whether a single active principle is present. These developments are paralleled by deeper insights into the pathophysiology of chronic and/or severe diseases. They are usually multifactorial and require a multitarget treatment. Drug combinations have become routine in the treatment of cancer, HIV or cardiovascular diseases. The selected drug combinations are based on the known mode of actions of each single drug. Their combinations in vivo are mainly empirical. Systematic screening of combinations of already approved drugs has started only recently. The potential of combining phytomedicine or natural products with synthetic drugs or introducing these into conventional treatment regimes are not yet systematically explored. This review presents recent examples of combination screenings. The screening for synergetic effects of such combinations is technically demanding and complex, also in the context of drug–herb interactions, but likely to substantially advance pharmacotherapy and future medicine.

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1. Introduction

According to current estimates about one third of drugs in clinical use are based on natural products. This includes constituents either directly isolated from natural products, synthesized or semi-synthesized by structural modification of their natural compounds [1]. Well known examples are colchicine, morphine, semi-synthetic aspirin, taxol and penicillin. Other antibacterial antibiotics include the cephalosporins or tetracyclines (for review see [2,3]). A more recent example is the development of artesunate from artemisinin. Artesunate is an antimalarial derivate of artemisinin from the Chinese medicinal plant *Artemisia annua* L., which also reveals profound anticancer activity in vitro and in vivo [4]. Today the WHO recommends parenteral artesunate as first line treatment in the management of severe falciparum malaria in African children [5]. Although this sounds like a success story, the present drug recovery appears rather moderate. This may be illustrated by the following figures: The mass bioprospecting effort of the national cancer institute of the United States screened about 114,000 extracts from an estimated 35,000 plant samples against a number of tumor systems [6]. A wide variety of compounds with different structures were isolated and characterized [7]. Clinically significant cancer chemotherapeutic agents that emerged from this project included paclitaxel (Taxols), topotecan (Hycamtins) and CPT-11 [8,9]. The latter two compounds are semisynthetic derivates of camptothecin from *Camptotheca acuminata* Decne., Nyssaceae [7,9]. However, often the source material has a good activity which is superior over the single constituents [29—32] raising the issue that it may not be a single active principle that is present and whether the screening protocols for drug discovery may need to be modified to consider synergistic effects.

These observations in drug development are paralleled by deeper insights into the pathophysiology of chronic and/or severe diseases. They are usually multifactorial and require a multitarget treatment. Thus drug combinations have become routine in today's treatment of cancer, HIV or cardiovascular diseases. It is assumed that drug combinations that address multiple targets simultaneously are better at controlling complex disease systems and are less prone to drug resistance [10,11].

2. Therapeutic approaches

Already in 1990 McCarty advocated the use of combinations of potentially valuable drugs rather than their sequential use [12] in the treatment of rheumatoid arthritis (RA). The argumentation was that the chronicity of RA reflects the failure to suppress multiple parallel pathologic pathways and an initial "broad spectrum coverage" might be a reasonable therapeutic approach [13]. The goals of drug combination therapies were obvious — improved efficacy, lower drug dosages and less drug toxicity. The provocative title of McCarthy's contribution in the J Rheumatol at that time was "*Suppress rheumatoid inflammation early and leave the (therapeutic) pyramide to the Egyptians*" [12]. The further developments in the treatment of RA demonstrated that he was right. In RA the combination of methotrexate (MTX) with a TNF-α-antagonist was shown to be more effective compared to the single applications [9,14]. Through combinations of Biologicals with MTX for the first time "drug free remissions periods" in RA patients have been achieved, the so called "drug holidays" [15,16].

The great potential of combination therapies can also be assessed from the results obtained by a multimodal treatment — the Bonn-Malmö-Protocol — for another autoimmune disease, the acquired hemophilia (AH). AH is an extremely rare condition in which autoantibodies (inhibitors) against clotting factor VIII induce acute and life-threatening hemorrhagic diathesis due to an abnormal blood clotting. In case patients suffer from AH alone, the treatment leads to a lasting complete remission in 92% of the cases [17,18]. The treatment protocol combines immunoadsorption of the inhibitor, with factor VIII substitution, intravenous immunoglobulin and immunosuppression with cyclophosphamide and prednisolone. The results of the long term follow-up of these patients allow to call it a cure of these patients [19]. Other common and more relevant indications in which drug combinations have become the standard regime are cancer chemotherapies or the treatment of HIV [10,11,20,21]. We see indeed today in conventional medicine a polypharmacology based empirically on the experience of the physician [22—24]. Thus a comparison of treatment approaches of traditional phytomedicine and conventional medicine reveals a conceptual approximation (Fig. 1). Nevertheless plant extracts possess specific properties.

However combination therapies remain until today not undisputed. A hot debate arose in the context of the so called "polypill", a combination of cardiovascular medications containing aspirin and agents to lower blood pressure and cholesterol ('polypills') to reduce cardiovascular disease [23]. A randomized placebo-controlled trial was undertaken with the Red Heart Pill (RHP, a polypill comprising a bilayered tablet containing aspirin 75 mg, lisinopril 10 mg, hydrochlorothiazide 12.5 mg and simvastatin 20 mg) or an identical placebo, in a 1:1 ratio with a duration of 12 weeks [23]. This polypill achieved sizeable reductions in the systolic blood