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Review

Synergy effects of herb extracts: Pharmacokinetics and pharmacodynamic basis

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ABSTRACT

Herbal medicine, especially traditional Chinese medicine and Ayurvedic medicine have played and still play an important role in fighting against various diseases. Emerging clinical studies regarding traditional Chinese medicine have provided convincing evidence for the first time to gain credibility and reputation outside China. Although synergistic therapeutic actions of herbal ingredients have been frequently reported, few reports have offered clear underlying mechanisms. This might be the main reason for the conflicting views with respect to the therapeutic efficacy of medicinal herbs. Therefore, this paper reviews the herb synergisms reported in the recent literature and discusses thoroughly the mechanisms underlying synergistic actions of herbal ingredients. The authors conducted an electronic literature search to detect articles published mainly in the last five years. Articles were included if they pertained to synergy research of ethnomedicines or the active compounds derived from them, included verification of synergy effects using modern analytical tools and molecular–biological methods. Results have revealed that the multi-component nature of medicinal herbs makes them particularly suitable for treating complex diseases and offers great potential for exhibiting synergistic actions. The mechanisms underlying synergistic therapeutic actions of herb medicines are (1): different agents may regulate either the same or different target in various pathways, and therefore cooperate in an agonistic, synergistic way; (2): regulate the enzymes and transporters that are involved in hepatic and intestinal metabolism to improve oral drug bioavailability; (3): overcome the drug resistance mechanisms of microbial and cancer cells; and (4): eliminate the adverse effects and enhance pharmacological potency of agents by “processing” or by drug–drug interaction. The exploration of synergistic mechanisms of herbal ingredients will not only help researchers to discover new phytomedicines or drug combinations but also help to avoid the possible negative synergy. Further clinical research is required for verifying these reported drug combinations and discovered synergistic mechanisms.

Abbreviations: TCM, traditional Chinese medicine; RC, Rhizoma Coptidis; HPLC–SPE–NMR, high-performance liquid chromatography–solid-phase extraction–nuclear magnetic resonance spectroscopy; TUNEL, terminal deoxynucleotidyl transferase dUTP nick end labeling; 5-HT, 5-hydroxytryptamina; PKC, protein kinase C; PKA, protein kinase A; MAPK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase; PC, phosphatidylcholine; FDA, US Food and Drug Administration; DTL, docetaxel; YCHT, yin-chen-hao-tang; ALT, alanine amino transferase; AST, aspartate amino transferase; ALP, alkaline phosphatase; MRT, mean residence time; SLC, solute carrier family; ABC, ATP-binding cassette; OAT, organic anion transporter; OATPs, organic anion-transporting polypeptides; P-gp, p-glycoprotein; BCRP, breast cancer resistance protein; CYPs, cytochrome P450 enzymes; MDR, multidrug resistance; ROS, reactive oxygen species.

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Contents

1. Introduction

The last decade has witnessed an emergence and rapid shift of the paradigm in chemotherapy, involving the gradual transition from the mono-substance therapy that had long been advocated with great vehemence to a multidrug therapy. This is mainly because of the ineffectiveness, resistance problems and side effects may appear when using synthetic mono-drugs, especially in the treatment of chronic diseases such as cancer, atherosclerosis, diabetes and inflammation [1]. The basis of using multidrug therapy for various disorders is the recognition that for each, more than one mechanism and gene is identified. For instance, a global genomic analysis has demonstrated 12 partially overlapping processes that are genetically altered in the great majority of pancreatic cancers. In addition, the pathway components that are altered in any individual tumor vary widely [2]. This has also been documented in the context of human glioblastoma multiforme, which is the most common and lethal type of brain cancer [3]. These results indicated that it is difficult to suppress cancer and other diseases by targeting a single gene or a single pathway that may alter amongst patients and that can be subject to mutations. These assays also lend credence to the use of a mixture of several drugs or herbs to achieve an overall therapeutic biological effect. Since many leading researchers have advocated using combination approaches to pursue the optimum therapeutic efficacy and to improve the patient's overall health status [4,5], the utilization of herbal medicine, which is considered as a “multi-target herb” [6], should be optimized.

As one of the largest biodiversity regions in the world, China has abundant medicinal and aromatic plant species, well documented traditional knowledge, a long-standing practice of traditional medicine, and the potential for social and economic development of medicinal and aromatic plants. Owing to their reduced side effects, high efficacy and a wide range of pharmaceutical activities, the use of TCM is gaining a reputation as a modern alternative to western medicine or as a complementary product to maintain health or treat aspects of diseases. Because the herb extracts consist of complex mixtures of major compounds, concomitant agents and other substances, the complex multi-component nature of medicinal herbs may serve as a valuable resource for network-based multi-target drug discovery due to its potential treatment effects by synergy. For instance, polyphenols and terpenoids are two groups of constituents which are contained in many plant extracts; the former possess a strong binding ability to different molecular structures like proteins or glycoproteins, while the latter have great affinities for cell membranes and therefore, a high potential to permeate through cell walls of the body or bacteria [7]. Epigallocatechin gallate (EGCG), the most abundant catechin in tea, is able to enhance the therapeutic efficacy of temozolomide in patients with glioblastoma. Chen et al. [8] have revealed that EGCG can cross the blood–brain barrier enough to cause chemosensitization in a mouse glioma model. When combined with temozolomide, EGCG could significantly reduce the expression levels of glucose-regulated protein 78 in temozolomide-treated animals, which is a key pro-survival component of the endoplasmic reticulum stress response system (EGCG alone did not provide survival benefit). Another interesting finding is that terpenes provided significant enhancements for the flux and cumulative amounts of the four model drugs. Among the tested terpenes, nerolidol provided the highest increase in the flux of the evaluated drugs. The flux of nicardipine hydrochloride, hydrocortisone, carbamazepine and tamoxifen were increased approximately 135-fold, 33-fold, 8-fold and 2-fold respectively [9]. Hence, under certain conditions, even polyphenols and terpenoids have not contributed directly to the pharmacological therapy achieved by the total herb extracts, but the polyvalence of these compounds can enhance the overall efficacy when co-administrated with other active compounds. *Rhizoma Coptidis* (RC), also known as Huang Lian, is extensively used by Chinese people for clearing heat as well as purging fire, resolving phlegm to activate meridians and promoting blood circulation to remove blood stasis. It is estimated that 1760 prescriptions, in 13 ancient prescription books before Chinese Song Dynasty, contained RC for the treatment of various diseases [10]. Previously, we recognized that the anti-diabetic effects of RC total extract were greater than alkaloid-rich fraction, thus the alkaloids including palmatine, berberine, coptisine, epiberberine, columbamine, jatrorrhizine and the minor polar constituents such as magnoflorine, ferulic acid and choline was purified from RC and the bioactivity of these compounds were preliminarily studied [11]. Modern pharmaceutical research have demonstrated that each of these compounds could mediate multiple