

Traditional Chinese Medicine (TCM): Are Polyphenols and Saponins the Key Ingredients Triggering Biological Activities?

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Abstract: The number of herbal formulae considered to be clinically effective and recorded in the Chinese medical literature is huge. The scientific basis for the remedial effects of these herbal formulae is not yet understood, nor has a clear need been given as to how to make use and combine traditional Chinese medicine (TCM) and Western medicine in an effective way. In this context, it is of interest to ascertain what individual constituents are responsible for the bioactive properties, and thus to extract the common characters of composition of huge formulae to provide a scientific explanation for their modes of action. We consider polyphenols and saponins as the key ingredients in TCM remedies responsible for most of the observed biological effects, reflecting the specific requirements within the TCM philosophy of treatment based on the investigation of its chemical composition.

With the emerging high throughput driven approaches and the recent experiences of combinatorial chemistry, the supply of chemical diverse compounds from natural sources is again receiving increasing attention in the drug discovery process [1]. In this context, traditional Chinese medicine (TCM) is presented as a powerful source, since the described biological activity profiles could be used as a pre-selection tool to rapidly identify potent bioactive compounds. Within this type of "ethnopharmacological driven search strategy" it is often ignored that, compared to current mainstream "Western" medicine, the theories of traditional Chinese medicine (TCM) appear abstract, and its concept is not scientifically understood. Whereas Western medicine originated from the study of anatomical structures in the human body and a natural science based on understanding of specific functions, TCM, evolved in ancient China, takes a very different, a philosophical, approach. It tends to focus on the function of the body in a holistic manner, and strives to maintain as well as restore functional balance (see Table 1) [2,3]. Although both, Western and traditional Chinese medicine, share the view that health is associated with homeostasis, TCM, in its application and theory, appears more appropriate to disease prevention and the handling of chronic conditions. This is strongly reflected by the TCM recipes, where different combinations of medicinal herbs and other sources, including insects, animals and minerals are formulated as ingredients. Typically, formulae are composed of multiple herbs, used in combination, so as to produce the desired therapeutic effect and reduce toxic side effects. How

to properly combine the herbs to make the formula effective is part of the fundamental knowledge of TCM. Most formulae are used for treating syndrome patterns instead of the TCM disease entities. Even in patients with the same disease, if they have different syndromes, they should receive different prescriptions. Through thousands of years of practice, a large number of herbal formulae have been developed and tested. The number of herbal formulae considered to be clinically effective and recorded in the Chinese medical literature is huge: 16 800, 20 000 and 61 739 formulae were described in *Taiping Royal Prescriptions* (AD 992), *General Medical Collection of Royal Benevolence* (AD 1117) and *Prescriptions for Universal Relief* (AD 1406), respectively. As mentioned above, one unique characteristic of TCM remedies is the combination of herbs, prepared in the formula for treatment. The principle of the combination is to pool different herbs that provide therapeutic action, decrease toxicity, improve pharmacokinetic and pharmacodynamic features, and increase absorption or modification of metabolism of the active components of key herb(s) that are essential for the treatment. The scientific basis of the remedial effects of these herbal formulae is not yet understood, nor has a clear need been given as to how to make use and combine TCM and Western medicine in an effective way. In this context it is of interest to ascertain what individual constituents are responsible for the bioactive properties, and thus to extract the common characters of composition of huge formulae to provide a scientific explanation for their modes of action.

We would like to propose in the following discussion an explanation for the effects of TCM based on the investigation of its chemical composition as a contribution to the improvement of the drug discovery process from nature.

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It is well known from the literature of plant metabolites, that polyphenols (including partial phenolics) and saponins (including part other glycosides such as iridoids glycosides) are present naturally in many herbs to the extent of being considered ubiquitous. They exhibit a rather broad spectrum of biological activities that can be summarized as following. Polyphenols constitute one of the most numerous and ubiquitous groups of plant metabolites. Ranging from simple phenolic molecules to highly polymerized compounds with high molecular weights, the occurrence of this complex group of substances in plants is extremely variable. Many of them have biological properties including antioxidant, anti-mutagenic, anti-oestrogenic, anti-carcinogenic and anti-inflammatory effects that might potentially be beneficial in human health, such as in the treatment and prevention of cancer, cardiovascular diseases, and other pathologies [4]. There is clear evidence that they have the potential to act in the three general areas specified (*i.e.*, transition metal ion complexation, as antioxidants in cellular pro-oxidant states, and by association with proteins and peptides) [5].

Table 1. Comparison between Western Medicine and TCM

	Western Medicine	TCM
Human body	Individual structure	Holistic Function
Objective	Treating disease and/or symptoms	Restoring homeostasis
Action	Fast; acute diseases	Gradual; chronic diseases
Drug	Single chemical	Mixture of herbs
Patient	Considered as a group	Individualized therapy

Triterpenoid and steroidal glycosides, referred to collectively as saponins, have considerable potential as pharmaceutical and/or nutraceutical agents in their natural form. Saponins, from a variety of sources, have been shown to have hypocholesterolemic, anti-coagulant, antiviral, anticarcinogenic, hepatoprotective, hypoglycemic, immunomodulatory, neuroprotective, anti-inflammatory and anti-oxidant activity [6,7].

Logically, plant extracts with these types of ingredients in sufficient concentration should be biologically active as well, in the same way as described above. We therefore statistically investigated the content of polyphenols and saponins in plants most often prescribed in formulae of traditional Chinese medicine. Data were obtained from the data bases, DNP (Dictionary of Natural Products on CD-ROM, Chapman&Hall, Version 8:2, February 2000), which describes the bulk of the published natural products, and China Pharmacopoeia [8], which covers the herbs most often used in traditional Chinese medicine. Over all, and most important, a total of 86% of those herbs investigated are reported to contain polyphenols and/or saponins in significant detectable amounts. In addition the herbs in the eight most famous and often used TCM herbal formulae are explicitly rich in polyphenols and/or saponins [9].

Traditional Chinese medicine often has multiple claims in terms of its therapeutic effects, which is explainable by the given properties of the multiple polyphenol and/or saponin constituents. In addition to the described specific biological properties as described above, and in a more general outline, polyphenols are known to inhibit virtually every enzyme that is tested *in vitro* at a given concentration [5]. The necessary association of polyphenols with proteins is discussed as an example of the very important biological phenomenon of molecular recognition. Present evidence strongly indicates that polyphenol complexations are largely of the "hand-in-glove" type. "Hand-in-glove" matching of donor and acceptor is both time-dependent and dynamic. Donor and acceptor are both time-dependent and dynamic. Donor and acceptor molecules are mobile and flexible and may assume a variety of shapes as complexation proceeds. Such associative processes frequently exhibit strong cooperative effects [10]. The association of polyphenols with proteins is principally a surface phenomenon. The efficacy of polyphenol binding to protein derives from the fact that polyphenols are multidentate ligands able to bind simultaneously via different phenolic groups at more than one point to the protein surface. At low protein concentrations the polyphenol associates at one or more sites on the protein surface, to give a monolayer that is less hydrophilic than the protein itself. Where protein concentration is high the relatively hydrophobic surface layer is formed by complexation of the polyphenol onto the protein and by cross-linking of different protein molecules by the multidentate polyphenols. This tendency to cross-link protein molecules at higher protein concentrations explains the changing stoichiometry of the associates with changing protein concentrations – an observation first hinted at by Sir Humphry Davy. More polyphenol is thus required to associate proteins from dilute solution than from concentrated solutions [10]. The progression of some diseases is known to be due to the off balance of the key pair(s) of enzymes that maintain the feedback loops that regulate the state of homeostasis in the body. One of the enzymes occurs at relatively higher, and another at relatively lower concentration. At the same doses, a polyphenol inhibits the concentrated enzyme more powerfully than the less abundant enzyme. It could therefore be speculated that a new state of homeostasis is established so as to prevent further progression or relieve some of the disease symptoms. Like polyphenols, the saponins also have non-specific bioactivities. Hence these active compounds may have more than one target of action, and thus are likely involved in multiple cellular pathways and tissues.

One of the key factors in the use of the Chinese medicine is the role of the solvent, water, and water solubility. As Szent-Gyorgi once cryptically remarked "Biology has forgotten water, or never discovered it". As known, the typical method of treatment for formulae prescribed by practitioners of TCM, is that the all materials are cooked with boiling water for several hours. Polyphenols and saponins generally have good aqueous solubility and are released thoroughly for the treatment; this results in rather high concentrations of the active ingredients as well as possible benefits regarding "cocktails" of natural products.

In summary we would consider the polyphenols and saponins as the key ingredients in TCM remedies responsible for most of the observed biological effects, reflecting the specific requirements within the TCM philosophy of treatment (see Table 1). This results in our assumption that most of the TCM herbs might be substituted by each other to a certain degree. As a consequence, identification of potent, specific and unique bioactive compounds from TCM knowledge appears limited; this requires alternative search and selection strategies for innovative natural products out of TCM remedies. On the other hand traditional Chinese medicine practices, with its diagnoses, and also prescription of medicines based on the individual conditions using a unique system that includes the spectrum of the variation of pulse, color of the eyes and tongue, and other symptoms in a rather holistic manner, offers a clear complement of health treatment. By relating this to the increased interest in the possibilities of investigation of complex molecular interactions of multiple components, and the corresponding simultaneous modulation by more than one compound, the broad knowledge of TCM will clearly remain an area of intensive research in the future.

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