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Historical perspective

Nanocarriers for the delivery of active ingredients and fractions extracted from natural products used in traditional Chinese medicine (TCM)

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ABSTRACT

Traditional Chinese medicine (TCM) has been practiced for thousands of years with a recent increase in popularity. Despite promising biological activities of active ingredients and fractions from TCM, their poor solubility, poor stability, short biological half-life, ease of metabolism and rapid elimination hinder their clinical application. Therefore, overcoming these problems to improve the therapeutic efficacy of TCM preparations is a major focus of pharmaceutical sciences. Recently, nanocarriers have drawn increasing attention for their excellent and efficient delivery of active TCM ingredients or fractions. This review discusses problems in the delivery of active TCM ingredients or fractions; focuses on recent advances in nanocarriers that represent potential solutions to these problems, including lipid-based nanoparticles and polymeric, inorganic, and hybrid nanocarriers; and discusses unanswered questions in the field and criteria for the development of better nanocarriers for the delivery of active TCM ingredients or fractions to be focused on in future studies.

Contents

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1. Introduction

Traditional Chinese medicine (TCM) plays an important role in modern health care because it is the basis for many clinical therapeutic agents used in Asian countries, which are also used as complementary or primary therapeutic agents in alternative medical systems worldwide [1,2]. According to the Registration Categories and Application Information Requirements of TCM and Natural Drugs issued by the China Food and Drug Administration, the raw materials in TCM preparations can be classified into the following types: active ingredients extracted from TCM materials, active fractions (sometimes termed "effective parts" [3]) extracted from TCM materials, TCM formulas (sometime termed TCM recipes [4] or TCM prescriptions [6]), or other forms exhibited in the regulations (http://www.sfda.gov.cn/WS01/CL0053/24529.html).

In traditional and current TCM application, TCM formulas that describe multi-component systems are used according to the syndrome differentiation theory of Chinese medical treatment. Due to the various shortcomings of conventional preparations, such as instability and the inconvenience of water decoction, new dosage forms are needed. However, new drug delivery systems for TCM formula delivery face significant challenges due to the complexity of the ingredients and their varying physiochemical and physiological properties. Few publications have explored the mechanisms underlying systemic treatment with TCM formulas [5], and thus the precise mechanisms mediating most of their effects in vivo remain unclear [6].

Active fractions are fractions extracted from a single plant, animal, or mineral, in which more than 50% of the composition of the fraction is made up of constituents responsible for its pharmacological activities [7]. Active fractions are easily obtained by extraction. The fractions reflect the unique features of TCM, such as compatibility, multiple components, and multi-target effects. In addition, quality standards for extracts ensure safety, efficiency, and specificity. Therefore, active fractions are widely used and extensively studied. For example, Veregen® ointment is a sinecatechin (from the active fraction of green tea leaves) formulation that was approved by the FDA in 2006. Benefiting from the success of this preparation, drug discovery programs based on active fractions have drawn much attention in recent years.

Similar to single compounds used as chemotherapeutic agents, active ingredients extracted from TCM possess well-defined physiochemical properties. Many well-known active ingredients such as artemisinin, arsenic trioxide, and curcumin have drawn significant attention due to their significant and promising physiological effects, which have been extensively demonstrated in mechanistic investigations.

Investigations based on nanocarrier-mediated drug delivery have been the focus of multiple fields of medical research, including disease treatment, diagnosis, and prevention [8], and have provided promising opportunities to address scientific issues once considered intractable. Nanocarriers have been used in the field of TCM preparations for two decades, but during the past decade, nanotechnology has markedly facilitated the development of TCM preparations. In recent years, numerous investigations have been carried out with the goal of developing nanocarriers for the delivery of active fractions or ingredients (Fig. 1). With improved understanding of nanocarriers and the properties of ingredients and fractions, the number of published results has increased progressively from year to year. Nanocarriers are an effective tool with which to overcome some limitations of TCM in clinical application, especially limitations in bioavailability and bioactivity in vivo and undesirable side effects. Their performance in delivering active ingredients and fractions is shown in Fig. 2. In this manuscript, we review reports published in the last 5 years on nanocarrier-mediated drug delivery systems for active ingredients and active fractions extracted from TCM.

2. Goals in the development of nanocarriers for active ingredients and fractions

2.1. Improvement of oral absorption and bioavailability

More than 50% of TCM preparations are administered by the oral route; however, low and variable bioavailability usually limits their clinical application, which is influenced by physicochemical properties, physiological barriers, and biochemical barriers such as poor water-solubility, poor permeability, poor stability, extensive metabolism in the enterocyte and hepatocyte, and rapid elimination [9–11] (Fig. 3). The poor bioavailability of active ingredients or fractions is usually due

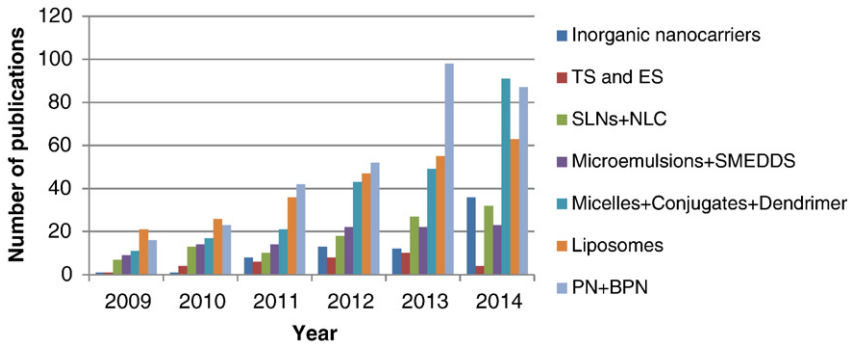

Fig. 1. Trends in the application of nanocarriers to deliver active ingredients and fractions (publications collected from Web of Science™ at http://apps.webofknowledge.com). Note: TS, transfersomes; ES, ethosomes; NS, niosomes; SLNs, solid lipid nanoparticles; NLC, nanostructured lipid carrier; SMEDDS, self-microemulsifying drug delivery systems; PN, polymeric nanoparticles; BPN, biopolymer-based nanocarriers.