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Preparation and evaluation of Paclitaxel and Brucea Javanica oil core-matched nanoemulsions to treat cancer *in vitro* and *in vivo*

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Abstract:

Objective Developed the core-matched nanoemulsions (CMNEs) to co-delivery paclitaxel-oleic acid prodrug (PTX-OA) and brucea javanica oil (BJO) for increasing the antitumor effect.. **Methods** Antitumor effects and mechanism of PTX-OA/BJO CMNEs that the combination therapy which based on core-matched technology (CMT) were evaluated *in vitro* and *in vivo*. **Results** The PTX-OA/BJO CMNEs were of nanoscale particle size (108.7 ± 2.3) nm and with entrapment efficiency of > 95%. The PTX-OA/BJO CMNEs displayed concentration and time-dependent cytotoxicity against HepG-2 cells and increased G_2/M phase block. More importantly, a significant reduction of the tumor volume with no obvious toxicity was observed in nude mice model following administration of PTX-OA/BJO CMNEs compared with the control treated with normal saline ($P < 0.05$), which suggested the excellent efficacy *in vivo*. It was further found that the enhanced effectiveness of PTX-OA/BJO CMNEs were associated with the ability of inducing apoptosis of the tumor cells, as well as obviously inhibiting tumor cell proliferation and the activity of TOPO Ⅱ. **Conclusion** Co-encapsulation of two drugs with different mechanisms allows simultaneous interruption of diverse anticancer pathways, resulting in increased therapeutic response and lower toxicity.

Keywords: brucea javanica oil; cancer; combination therapy; core-matched nanoemulsion; paclitaxel

1. Introduction

Cancer is one of the main causes of death worldwide, while most of patients need treatment with anticancer drugs in the metastatic chemotherapy and adjuvant (Woodward and Twelves, 2010; Huang et al, 2004). Paclitaxel (PTX), one of the most widely used anticancer agent, gets to hinder the microtubule network which is important for mitotic and interphase cellular functions. It also leads to the formation of stable microtubules and inhibits their disassembly, therefore, blocking cell proliferation and inducing eventual cell death (Gueritte et al, 1991; Ringel and Horwitz, 1991). However, as the majority chemotherapeutic regimens, the therapeutic response of PTX is often associated with serious side effects, including peripheral nervous system toxicity caused by insufficient selectivity (Azadeh and Razieh, 2012). Its limited tumor-bioaccessibility leads to large doses, inducing higher untoward toxicity and emergence of multidrug resistance (Iyer et al, 2005). In practice, PTX has been reported in combination with other chemotherapy agents, such as 5-fluorouracil, leucovorin, and cisplatin etc., in order to improve therapeutic response, reduce adverse effects, and reverse multidrug resistance etc (Nicholson et al, 2000; Danesi et al, 2010; Ma et al, 2014).

Brucea javanica oil (BJO) is an extract of the dried fruit of *Brucea javanica* (L.) Merr. As components of the unsaturated fatty acids of BJO, oleic and linoleic acids show specific affinity for tumor cell membranes and potent anticancer effects (Nie et al, 2012). Up to now, the reported study showed that BJO had the synergistic effects when combined with certain anticancer drugs or radiotherapy. Moreover, lots of clinical researches have showed that BJO microemulsion can cure alone for various cancers (Nie et al, 2012; Liu et al, 2001). According to Perry, drug combinations appeared to enhance the activity of each drug beyond additive influence. Pharmacologically, the selection of combinations is for synergies, avoiding antagonism and overlapping toxicities (Perry, 2008). As a result, we propose to design a drug delivery system which can safely, efficiently, and steadily co-delivery