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REVIEW

Chemical components, pharmacological properties, and nanoparticulate delivery systems of *Brucea javanica*

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Abstract: *Brucea javanica* has demonstrated a variety of antitumoral, antimalarial, and anti-inflammatory properties. As a Chinese herbal medicine, *Brucea javanica* is mainly used in the treatment of lung and gastrointestinal cancers. Pharmacological research has identified the main antitumor components are tetracyclic triterpene quassinoids. However, most of these active components have poor water solubility and low bioavailability, which greatly limit their clinical application. Nanoparticulate delivery systems are urgently needed to improve the bioavailability of *Brucea javanica*. This paper mainly focuses on the chemical components in *Brucea javanica* and its pharmacological properties and nanoparticulate formulations, in an attempt to encourage further research on its active components and nanoparticulate drug delivery systems to expand its clinical applications. It is expected to improve the level of pharmaceutical research and provide a strong scientific foundation for further study on the medicinal properties of this plant.

Keywords: *Brucea javanica*, chemical components, pharmacology, nanoparticulate delivery systems

Introduction

Brucea javanica, the ripe fruit of *Brucea javanica* (L) Merr (Simaroubaceae), was first mentioned in the Chinese medical monograph named Compendium of Materia Medica published in the sixteenth century.[1] It mainly exists in the tropical and subtropical zones of China, including Guangdong, Guangxi, Yunnan, and Fujian. The fruit of the *Brucea javanica* plant is characteristically ovate in shape, hard, and slightly apiculate at the apex with an approximate length of 6–10 mm and diameter of 4–7 mm. It is covered with protuberant reticulation and usually turns black or brown when ripe. Generally, the fruit is harvested in autumn and dried after removal of impurities.[2]

Actually, Brucea javanica is regarded as cold character and bitter taste, what laid the foundation for its various pharmacological properties. In Chinese medicine, *Brucea javanica* is characterized as an antipyretic and detoxifying plant, and widely used in the treatment of lung, prostate, and gastrointestinal cancer, and has potent antimalarial, anti-inflammatory, and antiviral effects, with low toxicity. Modern pharmacological research has demonstrated that tetracyclic triterpene quassinoids are the active ingredients in *Brucea javanica*,[3,4] and that the potential mechanism for antitumor efficacy lies in induction of apoptosis and decreasing cell proliferation by reducing expression of the *Bcl-2* gene.[3,4] *Brucea javanica* also enhances immune function.[5]

Increasing attention has been paid to the remarkable antitumor activity of *Brucea javanica* in recent years. In this paper, we discuss the chemical components of this

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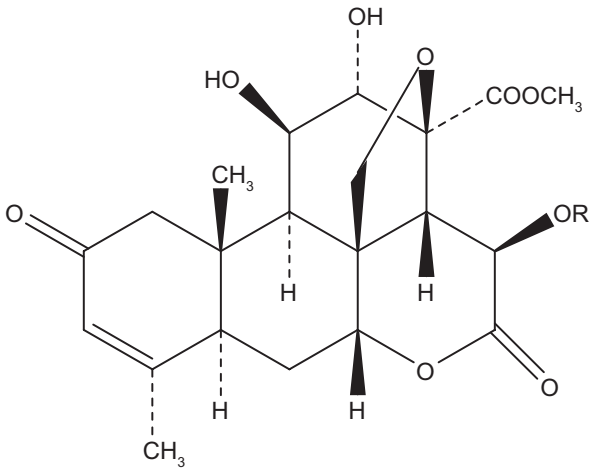

Figure 1 Basic structure of quassinoids.

medicinal plant, its pharmacological actions, and the prospect of developing nanoparticulate drug delivery systems, by presenting a summary of the relevant published literature on the active components of this plant and novel drug delivery systems containing *Brucea javanica*.

Chemical ingredients

Ever since the quassinoid compounds were first separated from *Brucea javanica* in 1967, more and more scientists have focused their research on the active ingredients of this plant and its antitumor activity.[6] During recent decades, with the help of modern analytic methods, such as ultraviolet and infrared spectroscopy, nuclear magnetic resonance, high-performance liquid chromatography, and mass spectroscopy, much progress has been made. Researchers have now isolated several natural components from *Brucea javanica*. These include the tetracyclic triterpene quassinoids,[7] anthraquinone, olein, oleic acid, linoleic acid,[8] pregnane glucosides,[9,10] and sesquiterpenes.[11] In particular, tetracyclic triterpene quassinoids are the main active ingredients of Brucea javanica with remarkable antitumor activity. The basic structure of the quassinoids is shown in Figure 1. It is based on a five-atom ring of C_8—CH_2—O—C_{13}, and is formed by three six-atom rings and a lactonic ring. According to recent research, the quassinoids have acted effectively in the treatment of several diseases. For instance, bruceoside A has good efficacy in leukemia and brusatol amarissima exert significant anti-inflammatory activity.[12] The quassinoids contain bruceine A, B, C, D, E, F, G, H, and I (Figure 2),[13,14] brusatol A,[15] dihydrobrusatol B,[16] bruceoside A, B, C, D, E, F, G, I, J, K, L, P, and S (Figure 3),[17–23] brusatol amarissima E2-glucosidase,[13] brusatol ketoacid, and bruceen.[24]

Pharmacological effects

Antitumor activity

Brucea javanica has been shown to have a variety of pharmacological actions, the most remarkable of which is its antitumor activity. *Brucea javanica* extract has shown a strong antitumor effect in S180 cells, with 24.6% inhibition of cell proliferation at high doses, while intermediate and low doses can prolong longevity by approximately 20% in tumor-bearing mice.[25]

Oleic acid, linoleic acid, and tetracyclic triterpene quassinoids all have antitumor activity, especially in lung, liver, ovarian, and cervical cancers. *Brucea javanica* inhibits cell proliferation by regulating the cell morphology and cycle, controlling apoptotic gene expression, and altering the process of cellular immunity.[5] The detailed antitumor mechanisms are summarized as follows. *Brucea javanica* can reverse drug resistance in tumor cells by altering P-glycoprotein on the cell membrane. For example, when drug-resistant ovarian cancer cells were exposed to an oily emulsion containing *Brucea javanica*, there was a dramatic decrease in the number of drug-resistant cells.[26] *Brucea javanica* can also inhibit the activity of topoisomerase II, thereby affecting DNA synthesis, leading to cell cycle arrest and apoptosis, eg, G0/G1 cell cycle arrest induced by *Brucea javanica* oil in hepatoma cells.[27] Further, cell cycle arrest and inhibition of DNA synthesis after *Brucea javanica* oil treatment was seen in the human SGC-7901 gastric carcinoma cell line, indicating apoptosis.[28] Meanwhile, a recent study has also provided strong evidence that *Brucea javanica* oil can induce apoptosis of cells via activation of caspase-8 and modulation of apoptosis-related proteins in human acute myeloid leukemia cell lines.[29] Generally speaking, patients with cancer are at risk of immunocompromise as a result of treatment with chemotherapeutic drugs. However, when used in combination with *Brucea javanica*, the safety and efficacy profiles of chemotherapeutic drugs improved, resulting in better immune function and quality of life in patients with late-stage lung cancer, mainly via increasing levels of T cells and natural killer cells.[30]

Anti-inflammatory activity

Traditionally, *Brucea javanica* has been used to treat amebic dysentery. Recent research has confirmed that *Brucea javanica* is also effective for malaria and other diseases with a parasitic

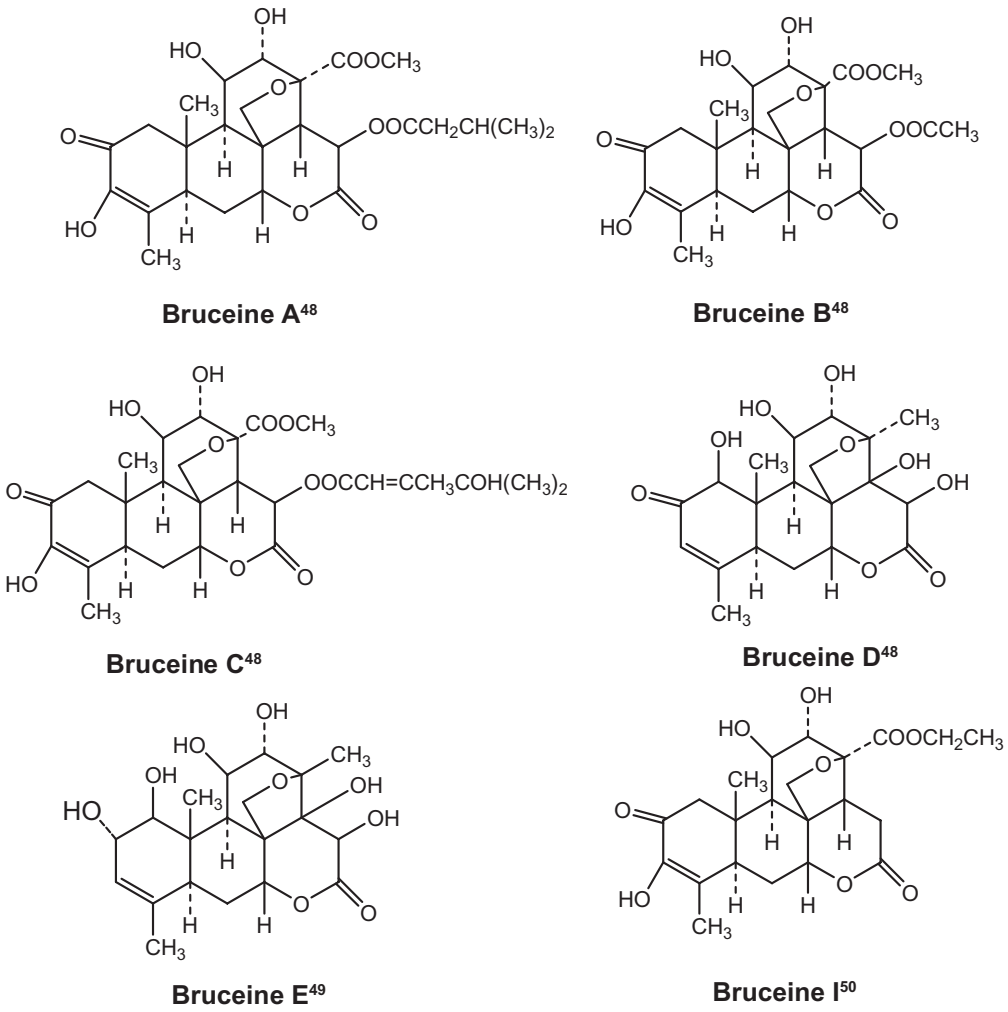

Figure 2 Structure of bruceine.

etiology. An ethanol-water extract of *Brucea javanica* relieved swelling caused by croton oil and granuloma induced by agar in a mouse ear model, indicating beneficial acute and chronic anti-inflammatory properties.[31] Remarkable efficacy was also observed in a rodent model of lung inflammation caused by sporozoites and in *Pneumocystis carinii* pneumonia.[32] *Brucea javanica* has also been used to prevent acute rectal inflammation and oropharyngeal mucosal inflammation induced by irradiation. However, the specific mechanism for this is not clear, so further comprehensive investigation is necessary.[33,34]

Antiviral activity

Brucea javanica has been used extensively to treat a variety of viral warts. It has showed significant corrosive ability in a range of wart types, including genital warts, flat warts, and corns. Flat warts are a skin disorder caused by human papillomavirus, and are amenable to treatment by *Brucea javanica*. This medicinal plant also triggers degeneration of tumor cells and nuclear condensation, eventually leading to cellular necrosis.[35] Clinical research indicates that infusion of *Brucea javanica* can be used to treat vulvar condylomata, with numerous advantages, including a rapid onset of action, convenience, low toxicity, and minimal irritation of the mucosal skin. Taking these favorable characteristics into consideration, *Brucea javanica* has a promising future in therapeutics.[36]

Nanoparticulate drug delivery systems

There are two advantages of using nanoparticulate drug delivery systems in Chinese medicine. One is that nanoparticulate drug delivery systems can prolong drug retention time, and the other is that they can control drug distribution in the body. Both advan-

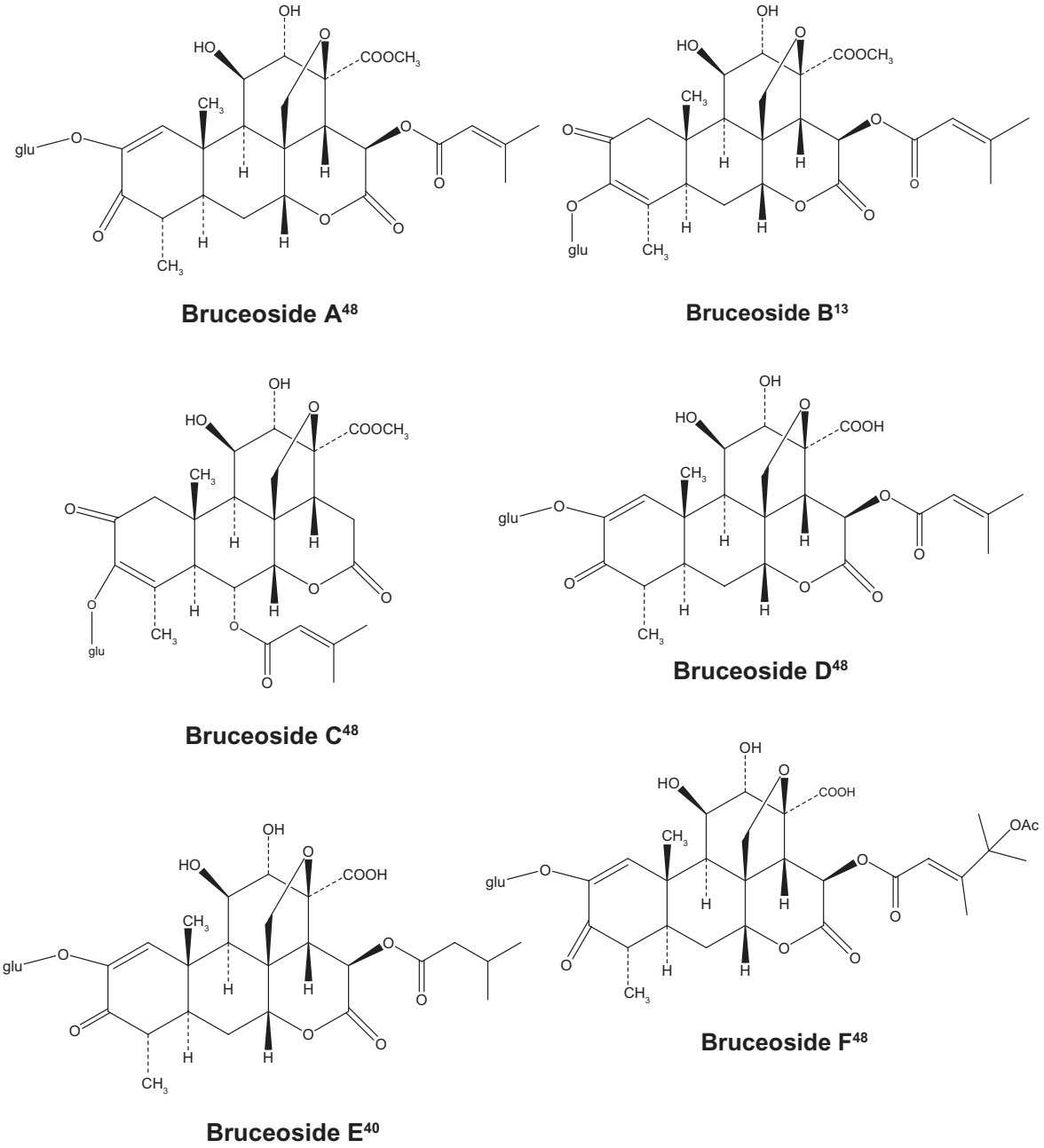

Figure 3 Structure of Bruceoside.

tages are beneficial for prolonging exposure time, increasing drug efficacy, reducing side effects, and overcoming the poor bioavailability of the main active components in *Brucea javanica* caused by poor water solubility. Presently, there are several nanoparticulate drug delivery systems for *Brucea javanica*, including liposomes, microemulsions, and nanoparticles.

Liposomes

A liposome is a microvesicle formed by a lipid bilayer and drug encapsulation. As a nanoparticulate drug delivery system, liposomes efficiently improve poor solubility by dissolving drugs, and generally has become a hot topic among researchers. The main components of the liposome, ie, phospholipids and cholesterol, are amphiprotic substances, which can not only encapsulate water-soluble drugs via a hydrophilic layer but also contain fat-soluble drugs via lipophilic materials. In this way, liposomes can enhance the water solubility and bioavailability of a hydrophobic drug. Furthermore, liposomes can reduce the effective drug dose and minimize toxicity, enabling a sustained therapeutic effect and improved safety. Xu et al identified that the optimal ratio of *Brucea javanica* oil to blank liposomes was 2.4:10 when manufacturing a freeze-dried solid liposomal powder of *Brucea*

javanica.[37] Other researchers combined membrane dispersal with freeze-drying technology in order to prepare a freeze-dried powder. Drug loading was 3.6% and encapsulation efficiency reached 92.4%. The stability of the freeze-dried product was quite good and when compared with injection of the oil emulsion, the liposomes containing *Brucea javanica* oil had stronger antitumor activity with less toxicity.[38] Further, some researchers have reported the effect of these liposomes on human hepatoma cells, indicating that they inhibited proliferation of HepG2 cells and induced apoptosis, which suggests good potential for liposomal *Brucea javanica* in antineoplastic therapy.[39]

Microemulsions

A self-emulsifying drug delivery system, such as a microemulsion, is a thermodynamically stable transparent solution which includes a drug, an oil phase, and nonionic surfactants. Broadening the contact area of the drug in the gastrointestinal tract, improving the bioavailability of hydrophobic drugs, and being able to serve as a carrier for a sustained controlled-release preparation, are all significant properties of self-emulsifying drug delivery systems. In addition, a microemulsion can mask the bad taste of a drug and improve its palatability. Researchers have identified that the optimal ratio of *Brucea javanica* oil to its excipients (Drug/Tween-80/TGFA) is 1:4:1 in terms of quality and stability.[40] Peng et al used the single factor method to find the optimal preparation method, and concluded that a temperature under 40°C is key to the stability of a microemulsion.[41] Other researchers explored the effect of several other components on quality, using soya lecithin as the surfactant, dioctanoyldecanoylglycerol as the oil phase, alcohol as the surfactant, and achieved enhanced bioavailability for an oral *Brucea javanica* oil microemulsion.[42] Further pharmacokinetic research showed that it took 6 hours to reach peak plasma drug concentrations after administration of a *Brucea javanica* oil microemulsion. This slow-release process indicated the feasibility of developing a controlled-release preparation.[43] Briefly, a microemulsion is characterized by targeted activity, a prolonged duration of action, and enhanced efficacy. Other researchers have reported that emulsifiers consisting of two thirds yolk lecithin and one third Poloxamer 188 show better stability with no delamination when centrifuged at 4000 rpm for 15 minutes.[44]

Nanoparticles

Nanoparticles have two possible shapes, ie, nanocapsules and nanospheres, both of which can be formed by natural, semisynthetic, or synthetic high-polymer material with a particle size between 10 nm and 100 nm. These particles show higher drug loading, a remarkable targeting effect, controlled release, and high stability, all warranting further research effort. Membrane-ultrasonic dispersion is a common method used for preparation of nanoparticles. Some researchers are using this method to produce solid nanoparticles with an entrapment efficiency of 82% and average particle size of 94 nm, accompanying with outstanding stability, and improved patient compliance with treatment.[45]

Other formulations

Emulsion and microencapsulation technology can also be used to improve water solubility and bioavailability. Gas chromatography has been utilized to determine the oleic acid and linoleic acid content in a microencapsulated preparation of *Brucea javanica* oil.[46] Beyond that, the features of a colon drug delivery system were investigated to prepare a soft *Brucea javanica* oil capsule using a coating technique in order to release the drug into the colon.[47]

Looking into the future

In recent years, as researchers have steadily intensified their study on antitumor mechanisms, *Brucea javanica* has been gradually arousing the interest of pharmacologists. However, various properties of *Brucea javanica*, including its water solubility, stability, and bioavailability are inadequate for it to be an effective treatment of cancer. Therefore, how to solve these problems and improve the curative properties of this medicinal plant are likely to become hot topics in the future. Some points are particularly important and should be noted. First, there is a need for further research on the active ingredients of *Brucea javanica* and the activated monomer mechanism. Second, it is necessary to separate and purify the active ingredients and the monomer. Third, we need to study the distribution and metabolism of the active ingredients in vivo. Last is the need to develop new nanoparticulate formulations for clinical use. With further investigation, *Brucea javanica*, one of the most active traditional Chinese medicines with significant antitumor activity, could be more widely used in the clinic and helpful to human health.

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Disclosure

The authors report no conflicts of interest in this work.

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