Phytochemistry xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Phytochemistry

journal homepage: www.elsevier.com/locate/phytochem

Review

Tetrandrine – A molecule of wide bioactivity

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ARTICLE INFO

Article history:
Received 16 October 2015
Received in revised form 2 February 2016
Accepted 7 February 2016
Available online xxxx

Keywords:
Stephania tetrandra
Menispermaceae
Tetrandrine
Pharmacological properties

ABSTRACT

Stephania tetrandra and other related species of Menispermaceae form the major source of the bisbenzylisoquinoline alkaloid – tetrandrine. The plant is extensively referenced in the Chinese Pharmacopoeia for its use in the Chinese medicinal system as an analgesic and diuretic agent and also in the treatment of hypertension and various other ailments, including asthma, tuberculosis, dysentery, hyperglycemia, malaria, cancer and fever. Tetrandrine, well-known to act as a calcium channel blocker, has been tested in clinical trials and found effective against silicosis, hypertension, inflammation and lung cancer without any toxicity. Recently, the efficacy of tetrandrine was tested against *Mycobaterium tuberculosis*, *Candida albicans*, *Plasmodium falciparum* and *Ebola* virus. Tetrandrine's pharmacological property has been proved to be through its action on different signalling pathways like reactive oxygen species, enhanced autophagic flux, reversal of multi drug resistance, caspase pathway, cell cycle arrest and by modification of calcium channels. The present review summarises current knowledge on the synthesis, distribution, extraction, structural elucidation, pharmacological properties and the mechanism of action of tetrandrine. Future perspectives in the clinical use of tetrandrine as a drug are also considered.

Contents

1. Introduction

Tetrandrine (Fig. 1) is a bisbenzylisoquinoline alkaloid (BBI) initially discovered in a Japanese medicinal plant, *Stephania tetrandra* S. Moore (Menispermaceae) by Kondo and Yano (1928), and confirmed by later researchers (Kubota, 1931; Chen and Chen, 1935). Subsequently, HPLC, LCMS and NMR techniques have been used to confirm the presence of tetrandrine in different species of plants from menispermaceae family (Huang et al., 2006; Koh et al., 2006; Liu et al., 2012a; Xie et al., 2014), including *Stephania hernandifolia* (Willd.) Walp. (Kupchan et al., 1961), *Cyclea peltata* (Kupchan et al., 1973; Kirana and Srinivasan, 2010; Pillai et al., 2010), *Cyclea barbata* (Guinaudeau et al., 1993), *Cocculus diversifolius* DC and

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http://dx.doi.org/10.1016/j.phytochem.2016.02.005
0031-9422/

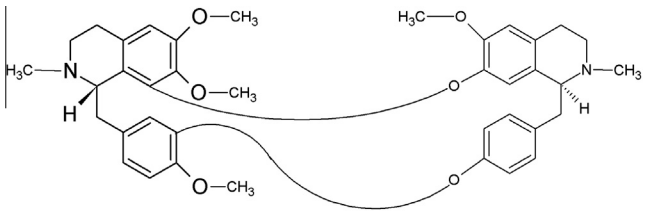

Fig. 1. Structure of tetrandrine.

Cocculus japonicus DC (Willaman and Schubert, 1961), *Cissampelos pareira* Var. hirsuta l. (Rojanasonthorn, 1970) and is now known from many other related species (Tringali, 2000). *S. tetrandra* is extensively referenced in the Chinese Pharmacopoeia and used in the Chinese medicinal system as an analgesic and diuretic agent and in the treatment of hypertension, as well as various other ailments (Huang and Hong, 1998; Tang and Eisenbrand, 1992), including asthma, tuberculosis, dysentery, hyperglycemia, negative ionotropic and chronotropic effects on myocardium, malaria, cancer and fever (Huang and Hong, 1998; Semwal et al., 2010; You-Ping, 1998).

The multiple ethnomedicinal uses of *S. tetrandra* stimulated interest in its natural product chemistry and the extraction, purification and characterisation of the active principle present in the plant led to the identification of the BBI alkaloid, tetrandrine. In its pure form, tetrandrine has been used to assess its role in pharmacological effects like fever, inflammation, cancer, diabetes, osteoclast differentiation, malaria, HIV and Ebola infection (Gulcin et al., 2010; Hristova and Istatkova, 1999; Sakurai et al., 2015; Takahashi et al., 2012). It has also been shown to act as a potent calcium channel blocker (Huang and Hong, 1998; King et al., 1988; Wang et al., 2004).

The present review draws together information on the extraction, structural elucidation, chemical synthesis, biosynthesis and pharmacological potential of tetrandrine. The problems and shortcomings in the use of tetrandrine as a drug are also considered, which might help in further understanding and modifying the use of the drug by the pharmaceutical industry.

2. Extraction and structural elucidation of tetrandrine

2.1. Extraction

Tetrandrine is mainly extracted from root samples of *S. tetrandra*, though it has been reported in other parts of the plant like leaf and stem. Chen and Chen (1935) extracted tetrandrine from powdered root samples of *S. tetrandra* by the alcohol percolation method. The alcoholic extract was concentrated, acidified and filtered. The filtrate was treated with sodium hydroxide to precipitate the alkaloid, which was recovered in crystalline form by precipitation from acetone.

Later, modifications of this procedure to fine tune the extraction process helped both in reducing the total time taken for the extraction and in increasing the yield. Kupchan et al. (1973) reported the extraction and purification of tetrandrine and several BBI alkaloids from a methanolic extract of *C. peltata* roots using column chromatography. An ionic liquid based ultrasound assisted extraction method was developed by Zhang et al. (2009b) to get a higher yield of tetrandrine from *S. tetrandra*. However, most methods include acid hydrolysis for the extraction and purification of tetrandrine from the methanol extract of *S. tetrandra* root samples (Carroll, 2011) and are essentially modifications of the method of Chen and Chen (1935). Herein, BBI alkaloids were extracted from the dried methanolic extract in benzene/toluene as thick oil and further precipitation of tetrandrine from acetone. However, the method failed to yield 100% pure tetrandrine. Recently, a better approach was developed for the purification of tetrandrine from the acid hydrolysed ethanolic extract of *S. tetrandra* root samples (Xie et al., 2014). The crude BBI alkaloid sample was then purified using C_{18} reverse phase flash chromatography system with 0.02% triethylamine in methanol as mobile phase. This method appears to be most suitable for the extraction and purification, as it yielded about 95% pure tetrandrine.

2.2. Structural elucidation

X-ray crystallographic studies of tetrandrine revealed a rough equilateral triangle shape of the crystal (Gilmore et al., 1976).

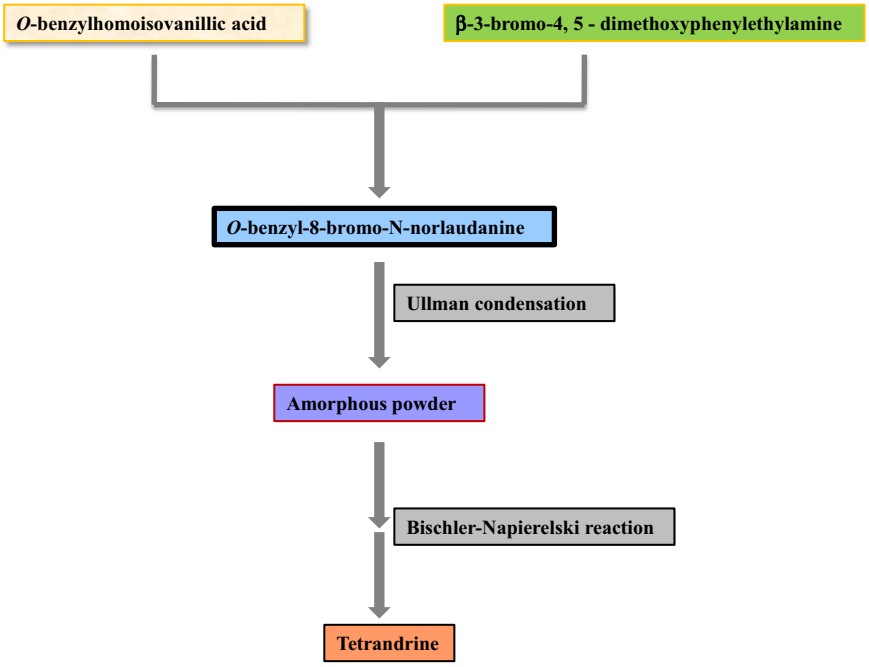

Fig. 2. Chemical synthesis of tetrandrine.

Please cite this article in press as: Bhagya, N., Chandrashekar, K.R. Tetrandrine – A molecule of wide bioactivity. Phytochemistry (2016), http://dx.doi.org/10.1016/j.phytochem.2016.02.005