Phytomedicine 23 (2016) 1511–1526

Contents lists available at ScienceDirect

Phytomedicine

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

Review

Gastrodia elata and epilepsy: Rationale and therapeutic potential

Mariana Matias[a,b], Samuel Silvestre[a,b], Amílcar Falcão[b,c], Gilberto Alves[a,b,*]

[a] *CICS-UBI – Health Sciences Research Centre, University of Beira Interior, Rua Marquês d'Ávila e Bolama, 6201-001 Covilhã, Portugal*
[b] *CNC – Center for Neuroscience and Cell Biology, University of Coimbra, 3004-517 Coimbra, Portugal*
[c] *Department of Pharmacology, Faculty of Pharmacy, University of Coimbra, Pólo das Ciências da Saúde, Azinhaga de Santa Comba, 3000-548 Coimbra, Portugal*

ARTICLE INFO

Article history:
Received 25 January 2016
Revised 29 August 2016
Accepted 3 September 2016

Keywords:
Epilepsy
Gastrodia elata
Gastrodin
Phenolic compounds
Anticonvulsant properties

ABSTRACT

Background: *Gastrodia elata* Blume (*G. elata*) is a traditional Chinese herb used for centuries in folk medicine. Due to the claimed anticonvulsant properties of *G. elata*, it is expected that this herb continues to be a target of research, aiming to deepen the available knowledge on its biological activity and safety.
Purpose: The current review aims to discuss the most recent advances on the elucidation of the phytochemical composition and anticonvulsant potential of *G. elata*.
Methods: Available literature was reviewed from PubMed, ISI Web of Knowledge and Science Direct, using combinations of the following keywords: Gastrodia elata, tianma, epilepsy, anticonvulsant and pharmacokinetics. Abstracts and full texts were evaluated for their clarity and scientific merit.
Results: *G. elata* rhizome, as well as specific phenolic compounds isolated from this herb, have demonstrated anticonvulsant potential in a variety of *in vitro* and *in vivo* models. The pharmacological mechanisms potentially involved in the anticonvulsant activity have been extensively studied, being similar to the known mechanisms claimed for the available antiepileptic drugs. In addition, the pharmacokinetics of the main bioactive component of *G. elata* (gastrodin) has also been studied.
Conclusion: Due to its recognised therapeutic properties, *G. elata* has gained an increasing interest within the scientific community and, therefore, new medicinal preparations containing *G. elata* rhizome itself or its bioactive components are expected to be developed in the coming years. Moreover, specific phytochemical constituents isolated from *G. elata* may also be considered to integrate programs of discovery and development of new anticonvulsant drug candidates.

Introduction

Natural products have been widely used as medicines, dietary products and nutritional supplements since ancient times due to the fact that they are a rich source of bioactive compounds and multiple benefits for human health have also been shown. Effectively, the use of medicinal plants has been validated by traditional use and they are time tested when compared with modern medicinal herbal supplements (Atanasov et al., 2015). For this reason, herbal plants and some of their bioactive compounds have come to highlight their therapeutic potential and have been the subject of extensive research (Kim et al., 2014), mainly at the level of their biological activities and the underlying molecular mechanisms of action. Consequently, natural products can represent valuable starting materials for drug discovery programs (Bauer and Brönstrup, 2014).

Gastrodia elata Blume (*G. elata*) is a traditional herb that has been used in oriental countries for centuries (Kim et al., 2012a, 2003b). Its dry tuber is officially listed in the Chinese Pharmacopoeia and has been used as an anticonvulsant, analgesic and sedative product (Ojemann et al., 2006). However, it has been described as having a large variety of other pharmacological properties. Additionally, several phytochemical compounds isolated from this herb, such as gastrodin, 4-hydroxybenzyl alcohol (HBA), vanillin, vanillyl alcohol, 4-hydroxybenzaldehyde, N^6-(4-hydroxybenzyl) adenine riboside (NHBA) and parishins, have been proposed as playing an important role in the pharmacological and

Abbreviations: AED, antiepileptic drug; AUC, area under the concentration-time curve; C_{max}, peak plasma concentration; CNS, central nervous system; ED_{50}, median effective dose; *G. elata*, *Gastrodia elata*; GABA-T, GABA transaminase; HBA, 4-hydroxylbenzyl alcohol; IC_{50}, median inhibitory concentration; i.v., intravenous; i.p., intraperitoneal; KA, kainic acid; LLOQ, lower limit of quantification; NHBA, N^6-(4-hydroxybenzyl) adenine riboside; p.o., oral (*per os*); scPTZ, subcutaneous pentylenetetrazole; SSADH, succinic semialdehyde dehydrogenase; SSAR, succinic semialdehyde reductase; $t_{1/2}$, elimination half-life; TD_{50}, median toxic dose.

* Corresponding author at: Faculty of Health Sciences, University of Beira Interior, CICS-UBI – Health Sciences Research Centre, University of Beira Interior, *Av.* Infante D. Henrique, 6200-506 Covilhã, Portugal. Fax: +351 275329099.
E-mail address: gilberto@fcsaude.ubi.pt (G. Alves).

http://dx.doi.org/10.1016/j.phymed.2016.09.001
0944-7113/

therapeutic properties claimed for *G. elata*. The majority of studies in this context has been focused on the potential interest for central nervous system (CNS) disorders as it has been recently reported (Jang et al., 2015). For instance, the treatment of dopaminergic SH-SY5Y cells with an ethanol *G. elata* extract showed protective effect on 1-methyl-4-phenylpyridinium-induced cytotoxicity (An et al., 2010) and similar results were observed with gastrodin (Jiang et al., 2014) and vanillyl alcohol (Kim et al., 2011). In *in vivo* conditions, using a Parkinson's disease mouse model, an aqueous *G. elata* extract revealed better antidyskinetic effects than those observed with amantadine, a reference drug (Doo et al., 2014). Regarding Alzheimer's disease, the ethyl ether fraction of a methanol *G. elata* extract reduced the amyloid-β peptide-induced cell death similarly to melatonin (Kim et al., 2003), and an aqueous extract improved cognitive functions in mouse and showed superior *in vitro* results than the observed with Gouteng herb and huperzine A (Mishra et al., 2011). Additionally, gastrodin decreased the area of amyloid-β peptide deposition in the cortex and hippocampus of Tg2576 transgenic mice (Hu et al., 2014) and 4-hydroxybenzyl methyl ether exhibited memory-ameliorating effects on SCH23390- and scopolamine-induced memory impairment models (Lee et al., 2015). Considering the treatment of cerebral ischemia, it has been reported an important neuroprotective effect of vanillin and HBA against ischemic neuronal cell death in the hippocampal CA1 region in gerbils subject to transient global ischemia (Kim et al., 2007). A long-term treatment of a rat model of Tourette's syndrome with gastrodin also revealed promising results, suggesting a dual restoring effect of gastrodin on the striatal dopamine content (Zhang and Li, 2015). Concerning psychiatric disorders, an aqueous extract of *G. elata* evidenced antidepressant-like effects possibly via regulation of serotonergic and dopaminergic systems (Chen et al., 2009) and this plant also showed potential benefits for the treatment of schizophrenia in the phencyclidine mouse model (Shin et al., 2010). An additional study also suggested anxiolytic-like effects for HBA and 4-hydroxybenzaldehyde (Jung et al., 2006) and NHBA appeared to potentiate the hypnotic effect of sodium pentobarbital in mice as an agonist for both adenosine A_1 and A_{2A} receptors (Zhang et al., 2012).

Beyond the CNS effects of *G. elata* constituents, many other pharmacological and therapeutic properties have been under investigation. For example, an ethanol extract of *G. elata* (Ahn et al., 2007) and vanillyl alcohol (Jung et al., 2008) inhibited the angiogenesis in the chick chorioallantoic membrane assay. Other *G. elata* extracts similarly showed potential in alleviating tumorigenesis and exhibited antimetastatic activity (Heo et al., 2007). In addition to its anti-angiogenic effects, vanillyl alcohol also inhibited the vascular permeability and exhibited anti-nociceptive activity probably through the involvement of prostaglandin biosynthesis (Jung et al., 2008). Moreover, vanillin was found to be a potent anti-inflammatory and analgesic compound, and 4-hydroxybenzaldehyde, HBA and benzyl alcohol significantly inhibited the cyclooxygenase-1 and cyclooxygenase-2 activities (Lee et al., 2006). The cardioprotective effects of *G. elata* have also been studied, mainly focusing on blood pressure and serum lipid levels, which were reduced by acidic polysaccharides purified from *Gastrodia* rhizomes in spontaneously hypertensive rats (Lee et al., 2012) and Sprague Dawley rats (Kim et al., 2012b). A reduction in insulin resistance was also observed in diet-induced obese rats treated with an aqueous *G. elata* extract, and this effect was mainly attributed to the phenolic compounds 4-hydroxybenzaldehyde and vanillin (Park et al., 2011). Furthermore, gastrodin significantly prolonged the coagulation time and decreased the fibrinogen content, suggesting its possible use as a promising anticoagulant lead compound (Liu et al., 2006); gastrodin also inhibited the cardiac hypertrophy induced by pressure overload in mice (Shu et al., 2012). A methanol extract of *G. elata* also presented gastroprotective effects (An et al., 2007) and, more recently, the anti-osteoporosis activity of gastrodin has also been explored (Chen et al., 2015a; Huang et al., 2015a).

The clinical evidence about the therapeutic properties of *G. elata* and/or its phytochemical constituents is still scarce. However, a double-blind, placebo-controlled clinical trial was already performed, suggesting an anti-sickling effect of vanillin (García et al., 2005). Another double-blind, randomized, controlled clinical study was carried out to investigate the preventive effects of gastrodin on the neurocognitive decline, a common complication after cardiac surgery with cardiopulmonary bypass; this study showed a significant decrease in the neurocognitive decline in the patients treated with gastrodin (Zhang et al., 2011). Moreover, a clinical study is ongoing to evaluate whether *G. elata* is effective in the treatment of masked hypertension (ClinicalTrials.gov, 2016).

Among the multi-pharmacological effects of *G. elata* and its bioactive constituents on the CNS, the anticonvulsant effects are certainly worthy of note (Ojemann et al., 2006). Indeed, epilepsy is one of the most common serious neurological disorders, affecting around 60 million people worldwide (Shetty and Upadhya, 2016); moreover, despite the large arsenal of antiepileptic drugs (AEDs) currently available, approximately 30–40% of patients develop pharmacoresistance (Kwan et al., 2010; Sørensen and Kokaia, 2013), thus existing an imperative need of new AEDs with improved efficacy. Furthermore, over the years, patients with epilepsy have used a variety of herbs to treat known comorbidities of epilepsy and common adverse events of AEDs (Ekstein, 2015), and some medicinal plants have shown potential as new treatment options for patients whose seizures are uncontrolled with the available AEDs. Actually, extracts of plants and/or their single constituents have shown to act on the same pharmacological targets as those of the most commonly used AEDs (Sucher and Carles, 2015; Zhu et al., 2014). Undoubtedly, the search for new anticonvulsant lead compounds among phytochemicals constituents has emerged as a promissory and alternative drug discovery approach. For instance, according to the progress report on new AEDs published as a summary of the Twelfth Eilat Conference (EILAT XII) that took place in Madrid (Spain) in 2014 (Bialer et al., 2015), at least three of the AED candidates in clinical development are herb-derived compounds (cannabidiol, cannabidivarin and huperzine A). Therefore, taking into account the contribution of Ojemann and collaborators (Ojemann et al., 2006) and the new literature available on the anticonvulsant properties of *G. elata* extracts and some of their phytochemical constituents, this review intends to address in a more extensively manner the phytochemical composition of *G. elata*, as well as discuss the more recent data on the pharmacokinetics and the scientific evidence for potential therapeutic benefits in epilepsy.

Methods

To prepare this review, an extensive literature search from three databases, PubMed, ISI Web of Knowledge and Science Direct, was performed to generate a critical but comprehensive overview of the phytochemistry, pharmacokinetics, pharmacological and anticonvulsant properties exhibited by crude extracts or purified compounds of *G. elata*. The keywords for the search consisted of combinations of the following terms: *Gastrodia elata*, tianma, epilepsy, anticonvulsant and pharmacokinetics.

Botanical aspects

G. elata, commonly known as "Tianma" (Ojemann et al., 2006), is a member of the Orchidaceae family (Tao et al., 2011). Although the orchids usually are famous due to their beautiful flowers,