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Pharmacology and toxicology of α- and β-Asarone: A review of preclinical evidence

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ABSTRACT

Background: Asarone is one of the most researched phytochemicals and is mainly present in the Acorus species and *Guatteria gaumeri* Greenman. In preclinical studies, both α- and β-asarone have been reported to have numerous pharmacological activities and at the same time, many studies have also revealed the toxicity of α- and β-asarone.

Purpose: The purpose of this comprehensive review is to compile and analyze the information related to the pharmacokinetic, pharmacological, and toxicological studies reported on α- and β-asarone using preclinical *in vitro* and *in vivo* models. Besides, the molecular targets and mechanism(s) involved in the biological activities of α- and β-asarone were discussed.

Methods: Databases including PubMed, ScienceDirect and Google scholar were searched and the literature from the year 1960 to January 2017 was retrieved using keywords such as α-asarone, β-asarone, pharmacokinetics, toxicology, pharmacological activities (*e.g.* depression, anxiety).

Results: Based on the data obtained from the literature search, the pharmacokinetic studies of α- and β-asarone revealed that their oral bioavailability in rodents is poor with a short plasma half-life. Moreover, the metabolism of α- and β-asarone occurs mainly through cytochrome-P450 pathways. Besides, both α- and/or β-asarone possess a wide range of pharmacological activities such as antidepressant, antianxiety, anti-Alzheimer's, anti-Parkinson's, antiepileptic, anticancer, antihyperlipidemic, antithrombotic, anticholestatic and radioprotective activities through its interaction with multiple molecular targets. Importantly, the toxicological studies revealed that both α- and β-asarone can cause hepatomas and might possess mutagenicity, genotoxicity, and teratogenicity.

Conclusions: Taken together, further preclinical studies are required to confirm the pharmacological properties of α-asarone against depression, anxiety, Parkinson's disease, psychosis, drug dependence, pain, inflammation, cholestasis and thrombosis. Besides, the anticancer effect of β-asarone should be further studied in different types of cancers using *in vivo* models. Moreover, further dose-dependent *in vivo* studies are required to confirm the toxicity of α- and β-asarone. Overall, this extensive review provides a detailed information on the preclinical pharmacological and toxicological activities of α-and β-asarone and this could be very useful for researchers who wish to conduct further preclinical studies using α- and β-asarone.

Introduction

The plant from the Acorus species, *Acorus calamus* Linn (Acoraceae), commonly known as “sweet flag”, has been widely used alone or in combination with other herbs in traditional Indian and Chinese medicine over centuries (Rajput et al., 2014). The other Acorus species such as *Acorus tatarinowii* Schott (Acoraceae) and *Acorus gramineus* Solander (Acoraceae) are renowned indigenous Chinese medicinal plants, officially listed in the Chinese Pharmacopoeia (Huang et al., 2013; Wang et al., 2014). The Acorus species are

Abbreviations: Aβ, β-amyloid peptides; AChE, Acetylcholinesterase; ATP, adenosine triphosphate; BDNF, brain-derived neurotrophic factor; Bcl, B-cell lymphoma; b.i.d, twice daily; CNS, central nervous system; CYP450, cytochrome P450; CREB, cAMP response element-binding protein; cDNA, complementary DNA; DNA, Deoxyribonucleic acid; EAAC1, excitatory amino acid carrier 1; EPM, elevated plus maze; GABA, gamma-amino butyric acid; HMGCR, 3- hydroxyl-3-methyl-glutaryl-coenzyme A reductase; HFD, high-fat diet; HDL, high-density lipoprotein; IL, interleukin; i.p., intraperitoneal route; i.v., intravenous route; JNK, c-jun N-terminal kinases; LC, light chain; LDL, low- density lipoprotein; LPS, lipopolysaccharide; MAO, monoamine oxidase; MMP, matrix metalloproteinase; MDR, multiple drug resistance; NMDA, N-methyl-D-aspartate; o.d., once daily; p.o., oral route; s.c., subcutaneous route; SAMP-8, senescence accelerated mouse-prone 8 mice; TST, tail suspension test; 5-HT, 5-hydroxytryptamine; 6-OHDA, 6-hydroxydopamine

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well-known for its traditional value for the treatment of respiratory disorders and various neurological disorders such as epilepsy and cognitive deficits (Rajput et al., 2014). On the other hand, *Guatteria gaumeri* Greenman (Annonaceae) is a traditional Mexican plant and its bark infusion has been indigenously used for the treatment of hypercholesterolemia and cholelithiasis (Chamorro et al., 1993).

The bioactive phytochemicals present in the rhizomes of the *Acorus calamus* Linn, *Acorus tatarinowii* Schott and *Acorus gramineus* Solander are alpha (α)- and, beta (β)-asarone, the quantity of which varies depending on Acorus species and origin (Hanson et al., 2005; Liao et al., 1998; Lim et al., 2012; Pandit et al., 2011; Park et al., 2011; Rajput et al., 2014; Zuo et al., 2012) and α-asarone being the main phytochemical present in the bark of the *Guatteria gaumeri* Greenman (Chamorro et al., 1999). Interestingly, it has been found that the *Acorus calamus* Linn, *Acorus tatarinowii* Schott, *Acorus gramineus* Solander and *Guatteria gaumeri* Greenman shares one or more similar pharmacological activities with α- and/or β-asarone such as antiepileptic (Bhat et al., 2012; Chen et al., 2013; Katyal et al., 2012; Liao et al., 2005; Limon et al., 2009; Pages et al., 2010), antidepressant (Chellian et al., 2016; Dong et al., 2014; Gu et al., 2010; Han et al., 2013; Ilaiyaraja et al., 2012; Pawar et al., 2012), anxiolytic (Lee et al., 2014; Liu et al., 2012b), neuroprotective (An et al., 2014; Cho et al., 2001; Limon et al., 2009; Muthuraman and Singh, 2012; Shukla et al., 2006; Zhang et al., 2014) or hypolipidemic (Hernandez et al., 1993; Medina-Franco et al., 2005; Parab and Mengi, 2002; Rodríguez-Páez et al., 2003) activities. These findings indicate that the pharmacological activities exhibited by the Acorus species or *Guatteria gaumeri* Greenman is mainly due to the presence of α- and/or β-asarone.

Consequently, both α- and β-asarone, the most studied bioactive phytochemicals have been reported to have a wide range of pharmacological activities, which can be potentially useful in the treatment of various diseases. In general, it is very important to consider the toxicity of any new chemical entities or drug even though it may be very efficacious and hence, therapeutics containing β-asarone is not recommended for the clinical use because of its toxicity (European-commission, 2002; JECFA, 1981). Numerous clinical studies in China had indicated the effectiveness of α-asarone against respiratory disorders and epilepsy (Feng et al., 2015; Zhang et al., 2010). However, there is no extensive critical review available on preclinical pharmacological and toxicological effects of α- and β-asarone in the literature. Hence, this review aims to summarize and discuss the preclinical study reports of α- and/or β-asarone with emphasis on its pharmacological and toxicological effects.

Method

An extensive literature search has been employed using the databases (PubMed, ScienceDirect and Google scholar) and relevant information from the year 1960 to January 2017 was retrieved. Besides, WHO expert committee on food additives and European commission reports on α-and β-asarone were assessed. The literature was searched using keywords such as α-asarone, β-asarone, pharmacokinetics, toxicology, pharmacological activities (*e.g.* depression, anxiety). This review is mainly focused to analyze published reports on pharmacokinetic, pharmacological and toxicological effects of α- and β-asarone using *in vitro* and *in vivo* studies. Furthermore, the molecular mechanisms involved in its pharmacological actions are elaborated.

Pharmacology of asarone: preclinical studies

Pharmacokinetics

The pharmacokinetic profile of α-and β-asarone is shown in Table 1.

Table 1
Pharmacokinetics of α-and β-asarone.

Species/strain/sex	Treatment	Sample analyzed	$t_{1/2}$ (h)	t_{max} (min)	C_{max} (mg/l)	AUC 0- ∞ (mg/l*h) mg/l* min	Kel (l/h)	Vd (l/Kg)	CL (l/h/Kg)	Reference
Dutch belted rabbits/ male and female	β-asarone (30 mg/kg, i.v.)	Plasma	1.380	–	–	5.989	0.48	9.979	4.98	(Fang et al., 2012a)
		Cerebral Cortex	1.937	60	1.525 ± 0.788	5.495	0.358	15.261	5.459	
		Cerebellum	8.149	60	2.257 ± 0.426	15.577	0.085	22.649	1.926	
		Thalamus	2.832	60	0.861 ± 0.234	4.561	0.245	26.879	6.578	
		Brain stem	7.142	60	1.719 ± 0.674	11.519	0.097	26.842	2.604	
		Hippocampus	1.300	60	2.369 ± 1.517	7.201	0.533	7.814	4.166	
Wistar rats/male	α-asarone (20 mg/kg, i.v.)	Plasma	1.589 ± 0.41		6.876 ± 1.502	3.829 ± 0.440	–	–	5.28 ± 0.66	(Chunjuan et al., 2011)
C57BL6 mice/ male	α-asarone (10 mg/kg, i.p.)	Plasma	0.0698	–	–	–	–	–	–	(Kim et al., 2015)
		Brain	0.3181	–	–	–	–	–	–	
C57BL6 mice/ male	α-asarone (10 mg/kg, p.o.)	Plasma	0.1755	–	–	–	–	–	–	
		Brain	0.4736	–	–	–	–	–	–	

i.v., intravenous route; i.p., intraperitoneal route; p.o., oral route; $t_{1/2}$, half-life; C_{max}, peak concentration; t_{max}, time at which C_{max} occurs, AUC, area under the curve; Kel, elimination rate constant; Vd, volume of distribution; Cl, clearance; -, unknown.