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Review article

Therapeutic potential of songorine, a diterpenoid alkaloid of the genus *Aconitum*

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ABSTRACT

Alkaloids are well-studied secondary metabolites, with recent preclinical studies evidencing that many of them exhibit anti-cancer, anti-depressant, anti-nociceptive, anti-inflammatory, anti-pyretic, anti-platelet, anti-oxidant, and anti-bacterial properties. Aconitum is a genus rich of diverse alkaloids. More than 450 alkaloids have been identified in a variety of species. Songorine is a C_{20} diterpenoid alkaloid and 12-keto analog of napelline, isolated from *Aconitum soongaricum* and was associated with a heterogeneous panel of biological functions. However, the bioactivity profile of this natural product has not been reviewed up to now. The present manuscript aims to summarize the most important biological activities associated with songorine administration in preclinical models. The most significant data found in the scientific literature were evaluated in order to summarize the potential clinical utility of songorine in a diverse spectrum of pathologies and conditions. Songorine and its derivatives have many pharmacological effects including anti-arrhythmic, anti-cardiac-fibrillation, excitation of synaptic transmission, anxiolytic effects, anti-nociceptive, anti-inflammatory, anti-arthritis effects, and a regenerative effect in a skin excision wound animal model. Despite its outstanding pharmacotherapeutic potential, songorine has never been tested in clinical trials. Therefore, further evaluation is required to better evaluate its clinical utility.

Contents

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Abbreviations

ED_{50}	Median effective dose
LD_{50}	Median lethal dose
AAI	Antiarrhythmic index
CNS	Central nervous system
GABAA	γ-Aminobutyric acid A
NSAIDS	Nonsteroidal anti-inflammatory drugs
PI3K	Phosphoinositide 3-kinase
ERK1/2	Extracellular signal-regulated protein kinases 1 and 2
JNK	c-Jun N-terminal kinase
NF-κB/IKK	Nuclear factor-κB/IκB kinase
TNF-α	Tumor necrosis factor alpha
IFN-γ	Interferon gamma
IL	Interleukin
SOD	Superoxide dismutase
GPx	Glutathione peroxidase
MMPs	Metalloproteinases

1. Introduction

Phytopharmaceuticals have played an important role in the history of medicine and, to this day, they are considered an integral part of our health care system [1–4]. Despite the great advances of modern therapeutics, phytopharmaceuticals continue to play crucial role in the treatment of various disorders [5,6]. Additionally, many modern drug classes must deal with problems related to efficacy and therapeutic resistance [3,7–9]. Natural compounds could therefore represent a viable option for developing therapies due to their vast chemical diversity [10].

Alkaloids are among the most widely distributed plant-derived secondary metabolites [11,12]. Several alkaloids and their derivatives have been used clinically to treat a variety of medical disorders. Similarly, numerous alkaloids have marked preclinical effects including anti-platelet [3], anti-cancer [13], anti-inflammatory [6] antibacterial [14], anti-depressant [15], and anti-oxidant properties [16]. However, further evaluation is required to make a smooth transition to clinical applications.

Aconitum is a genus member of the Ranunculaceae family very rich in alkaloids. In this sense, more than 450 alkaloids have been identified in various *Aconitum* species [17]. Also, over 40 alkaloids have been described in *Aconitum carmichaelii* alone [18]. Songorine is an alkaloid mainly present in *Aconitum soongaricum* L. which absolute configuration was first solved by Okamoto et al., in 1965 [19,20]. In a later study, songorine was also found in the mother and lateral roots of *Aconitum carmichaelii* Debx, but not in *Aconitum kusnezoffii* Reichb [21]. It is a C_{20} diterpenoid alkaloid and a 12-keto analog of napelline [22]. Members of the *Aconitum* family plants possess properties amendable to the treatment of pain, inflammatory processes, coldness of extremities, and metabolic dysfunction [22,23]. In fact, in the traditional Chinese and Japanese medicine diverse preparations from *Aconitum* roots have been widely used to treat many disorders [24,25]. This review focuses on the diverse biological activities of songorine (Fig. 1) and its prospects for future clinical applications.

2. Antiarrhythmic activity of songorine in *in vivo* models of experimental arrhythmia

Dzhakhangirov et al. (1997) studied the antiarrhythmic properties of a large number of diterpene alkaloids, including songorine [26]. In the performed animal studies, antiarrhythmic properties were tested in the models of aconitine arrhythmia in anesthetized rats and of irreversible cardiac fibrillation in alert mice. Songorine displayed significant anti-arrhythmic effects both in rats and mice. The median effective dose (ED_{50}) was 7.3 mg/kg while the median lethal dose (LD_{50}) was 142.5 mg/kg in rats. Marked anticardiac-fibrillation action was elicited in mice with ED_{50} of 25 mg/kg and LD_{50} of 480 mg/kg. In a study using isolated rat cardiomyocyes it has been reported that the treatment with ryanodine induces an increase in the intracellular concentrations of calcium (Ca^{2+}) from the sarcoplasmic reticulum [27]. Treatment with songorine blocks the liberation of Ca^{2+} in cardiomyocyes and this, can be associated with the antiarrhythmic effects of the compound. Various songorine analogues also produced a wide range of diverse effects. Shakhidoyatova et al. (2001) synthesized a series of songorine derivatives and evaluated their antiarrhythmic properties in the aconitine-induced arrhythmia model in rats [28]. It was evidenced that mono-aromatic ester substitution potentiates the effects of songorine, but instead, free hydroxyl groups are crucial for the antiarrhythmic effects since benzoylation of these groups results in the loss of the activity [26]. Songorine and its derivatives exhibit significant antiarrhythmic effects and favorable safety profile (Scheme 1 and Table 1).

3. Central nervous system (CNS) stimulatory effects upon songorine administration

Songorine has been reported to exert stimulatory effects in *in vivo* studies that has been associated with the dopaminergic system. Ameri (1998) studied the effect of alkaloids on synaptic transmission in rat hippocampus [22]. At a concentration of 10–100 μM, songorine caused excitatory synaptic transmission in a dose dependent manner. Dopamine D1 receptor antagonists do not antagonize this transmission. However, sulpiride (0.1 μM) and haloperidol (10 μM), both selective D_2 receptor blockers, inhibit this synaptic excitation. Stimulation of the CNS by alkaloids is well established [29,30]. A stereotypic head rocking motion in cats that were administrated 50-100 mg/kg of songorine has been described [22,31]. Similarly, pretreatment with songorine *in vivo* blocked the sedative-like action of bulbocapnine, a dopamine receptor antagonist [22]. Zhao et al. (2003) have studied songorine's impact in rat hippocampal neurotransmission in order to shed light on the mechanisms governing excitatory synaptic transmission [17].

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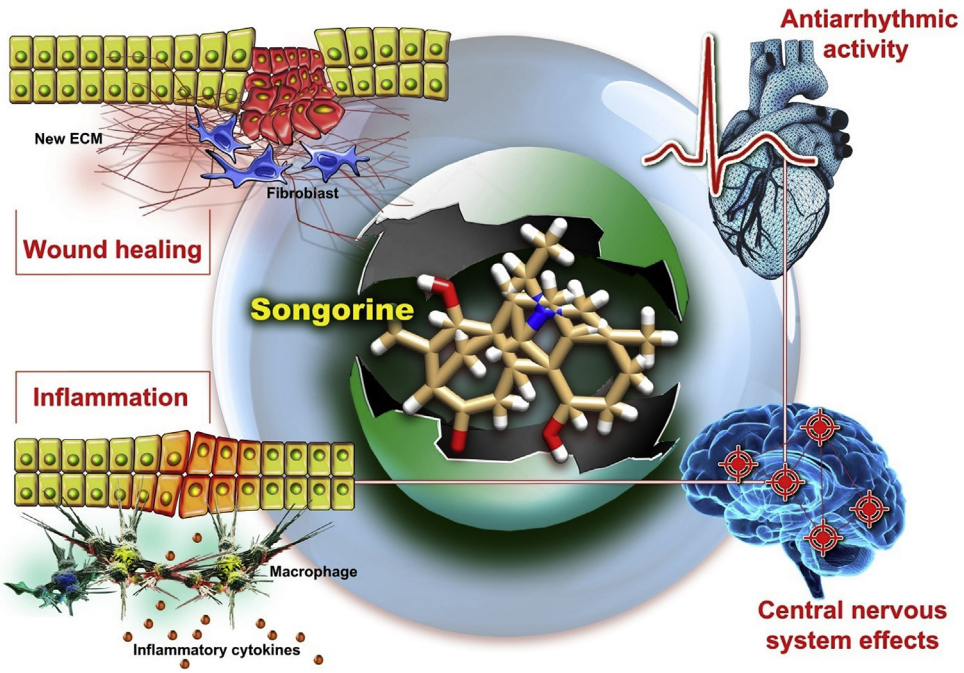
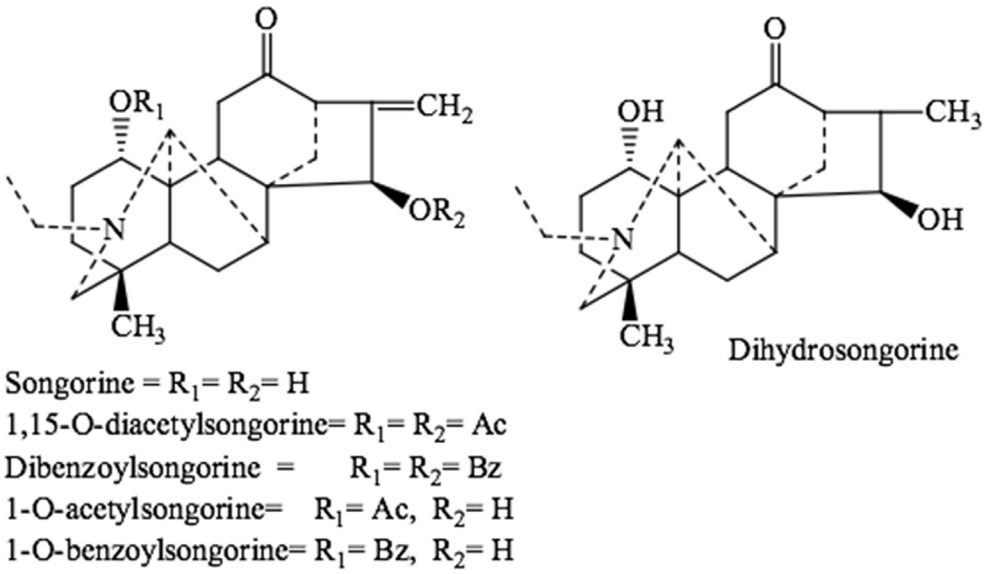


Fig. 1. Biological effects of songorine.



Scheme 1. Chemical structure of songorine and selected songorine analogues.

Table 1
Antiarrhythmic activity of the synthesized compounds on the aconitine-induced arrhythmia model in rats [28].

Compound	LD_{50} (mg/kg)	ED_{50} (mg/kg)	AAI = ED_{50}/LD_{50}
Songorine	142	7.3	19
1,15-O-diacetylsongorine	131	18	7.3
1-O-acetylsongorine	150	15	10
1-O-benzoylsongorine	41	0.38	107.9

Profound inhibition of γ-aminobutyric acid A (GABAA) in rat hippocampal neurons was observed, which provided the mechanistic evidence for songorine as a GABAA receptor antagonist in the brain of rats.

Anxiolytic effect upon pretreatment with songorine (0.25 mg/kg) was also reported in mice, with the effect of the compound even exceeded the action of the positive control phenazepam. However, songorine was devoid of sedative effects increasing the approaches to drinkers, locomotor activity and rearings, in contrast to phenazepam which significantly decreased all these parameters respect to the control group [32].

4. Songorine is associated with analgesic effects and also anti-inflammatory properties

The analgesic effects of songorine alkaloid can derive from the potentiation of central and peripheral mechanism. Nesterova et al.

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(2014) isolated songorine from *Aconitum baikalensis* and evaluated its central anti-nociceptive effects in animal models [33]. Songorine demonstrated marked antinociceptive effects in an acetic acid induced cramp test that was antagonized by naloxones (opioid receptor nonselective antagonist) suggesting the existence of affinity for opioid receptors for antinociceptive like effect.

Also, the peripheral anti-inflammatory properties of songorine were confirmed using a carrageenan-induced inflammation assay [34]. Moreover, the compound also demonstrated marked anti-inflammatory effect following sub-plantar arachidonic acid injection. Most synthetic analgesic and anti-inflammatory drugs such as NSAIDS, are associated with gastrointestinal ulceration [35,36], but interestingly songorine was found to be free of gastrointestinal side effects and may, therefore, prove to be superior in efficacy and safety when compared to currently used analgesic and anti-inflammatory drugs. In this connection, new drug discovery approaches may consider it as a potential candidate for further detail studies.

The administration of natural compounds in arthritis and rheumatoid disorders has been increasingly evaluated as potent therapeutic options for these pathologies due to their wide availability, low costs and also minimal side effects. The observed anti-inflammatory properties often consist in downregulation of key cytokines like TNF-α and IFN-γ, but also inflammatory interleukins (IL-1α/2/6/8/12). Increased evidences associates arthritis and rheumatoid disorders with elevated oxidative stress with consequences on the accumulation of oxidant and free radicals, whereby natural agents are potent inhibitors through their antioxidant properties. The proposed mechanisms consist in stimulation of antioxidant enzymes like SOD, catalase and GPx and also decrease of free radicals levels. Moreover, these beneficial roles are often completed by the ability of alkaloid compounds to counteract the activity of matrix metalloproteinases (MMPs) that normally are involved in matrix degradation (e.g., MMP-3, MMP-9) and are increasingly active in arthritis and rheumatoid conditions. Many of these pathologies are associated with pain and also disabilities caused in part by the increased amount of discomfort. Interestingly, some medicinal plants are also activating pathways being associated with pain alleviation and resulting analgesic and anti-nociceptive properties [37,38]. Songorine and also other natural drugs are emerging as potent alternatives for inflammatory and pain-causing disorders with minimal negative side effects. Even so, the restrictive number of clinical trials is partially impairing the recognition of these agents as therapeutic tools, since the majority of the experimental research is so far conducted on *in vitro* or *in vivo* models.

5. Mechanisms behind the increased would healing properties of songorine (regenerative properties)

Zyuzkov and colleagues (2012) studied the regenerative effects of diverse diterpene alkaloids including songorine using a mouse skin wound model [39]. By day 3 after the wound infliction, songorine alredy showed significant regenerative action, and complete regeneration of the skin was observed by day 14 (for comparison, in the control animals the wounds healed by day 18 of the experiment). Songorine treatment reduced already by day 3 the leukocyte infiltration at the wound edges, derma, and in the underlying tissues. The underlying mechanism for this healing effect is thought being mediated by the profound action on resident precursor cells. Of the tested diterpene alkaloids, songorine was found to have the most prominent effect on wound healing. In a further study by the same group, treatment with songorine also increased the fibroblast content in the granulation layer using the same mouse skin wound model [40]. The addition of songorine *in vitro* to the culture medium results in a significant stimulation of mesenchymal precursor cells (CFU-F). The mechanism of action of this activation was mediated by fibroblast growth factor (FGF) receptors, since the addition of anti-FGF receptor antibodies blocked this activation. Additional assays also evidenced that Inhibitors of PI3K, ERK1/2, and p38 interfere with the increase proliferative activity of mesenchymal progenitor cells associated with songorine treatment. ERK1/2 and p38 inhibitors also impeded cell differentiation [41]. The application of specific inhibitors of JNK and p53 enhanced stimulation of fibroblast colony/cluster formation and proliferative activity of mesenchymal precursor cells treated with songorine [41]. Further, mechanistic studies performed on NF-κB/IKK-mediated signaling have demonstrated that toridonin, a NF-κB inhibitor, prevents the proliferation and differentiation of mesenchymal progenitor cells induced by songorine treatment. Additionally, aurothiomalate, an IKK-2 blocker, inhibits the mitotic activity of fibroblast precursors without changing the rate of cell differentiation [23,42]. Finally, the same group also proved that adenylate clyclase also participates in the stimulation of proliferation of mesenchymal progenitor cells since its blockade leads to significant decrease of CFU-F [43] Since songorine activates mesenchymal progenitor cell proliferation and differentiation, it is an attractive natural compound that may be used in future mesenchymal progenitor cell-based therapies.

6. *In vivo* pharmacokinetic studies involving songorine administration

In 2015, Dong et al. developed a novel quantification method evaluating the pharmacokinetics of songorine [44]. This simple method involves the use of ultra-performance liquid chromatography tandem mass spectrometry to analyze the pharmacokinetic properties of songorine in rat plasma. Following the intravenous administration of songorine at a concentration of 5 mg/kg, mean maximum plasma concentration was 654.79 ng/mL and the elimination half-life was 0.94 h. The initial rapid decline in the plasma concentration after songorine administration indicated that possibly the compound might have been distributed in various physiologic compartments beyond the plasma.

7. Aconite detoxification and safe administration of songorine

Aconite, a source of songorine, is well known for the beneficial effects of the related extracts, but also recognized as a toxic material that needs to be subjected to prior detoxification in order to be safe for human administration. For the moment, there are different purification methods, but even so, the workflow results in a significant lost of the active alkaloids with therapeutic value. A recent article demonstrated a new and improved method based on a one-step approach for detoxification that involves only cutting and drying of the compound [45]. Besides the major time parameters improving (10 h instead of days), there are also other advantages like high components percentages, quality consistency and also lack of heavy metals. Determination of the method superiority was done via HPLC and UHPLC/Q-TOF-MS quantifications and also multivariate analysis for product quality [45].

8. Conclusions and future prospects

Songorine is an aconitine alkaloid with notable pharmacological effects and promising preclinical potential. As such, it possesses antiarrhythmic, anti-anxiety, antinociceptive, anti-inflammatory properties as well as regenerative effects. The main limitation for its therapeutic use is the lack of clinical investigations that allow confirmation by promising results observed in animal models. Further evaluation of the mechanisms underlying these beneficial

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properties and a detailed assessment of its safety profile are also required for a better assessment of its potential for future clinical applications.

Conflicts of interest

The authors declare that they have no competing financial interests.

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