



The relaxant effect of *Ferula assafoetida* on smooth muscles and the possible mechanisms

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ARTICLE INFO

Article Type:

Review

Article History:

Received: 29 September 2014

Accepted: 3 January 2015

Keywords:

Ferula asafoetida

Extract

Oleo-gum-resin

Smooth muscle

Relaxant effect

ABSTRACT

Asafoetida (*Ferula asafoetida*) an oleo-gum-resin belongs to the Apiaceae family which obtained from the living underground rhizome or tap roots of the plant. *F. assa-foetida* is used in traditional medicine for the treatment of variety of disorders. Asafoetida is used as a culinary spice and in folk medicine has been used to treat several diseases, including intestinal parasites, weak digestion, gastrointestinal disorders, asthma and influenza. A wide range of chemical compounds including sugars, sesquiterpene coumarins and polysulfides have been isolated from this plant. This oleo-gum-resin is known to possess antifungal, anti-diabetic, anti-inflammatory, anti-mutagenic and antiviral activities. Several studies investigated the effects of *F. asafoetida* gum extract on the contractile responses induced by acetylcholine, methacholin, histamine and KCl on different smooth muscles. The present review summarizes the information regarding the relaxant effect of asafetida and its extracts on different smooth muscles and the possible mechanisms of this effect.

Implication for health policy/practice/research/medical education:

foetida and its essential oil on different types of smooth muscle on contracted tissues induced by various contractile agents have been shown. The different mechanisms of relaxant effects of *F. assa-foetida* including inhibitory effects of muscarinic receptors and histamine (H₁) receptors as well as β -adrenoceptors stimulatory effects on calcium channels have also been reported. It might be beneficial spastic conditions.

Please cite this paper as: Khazdair MR, Boskabady MH. The relaxant effect of *Ferula assafoetida* on smooth muscles and the possible mechanisms. J HerbMed Pharmacol 2015; 4(2): 40-44.

Introduction

Asafoetida (*F. asafoetida* L.) belongs to the Apiaceae family which is obtained from the exudates of the living underground rhizome or tap roots of the plant. *F. asafoetida* or gum-resin is known as “Anghouzeh”, “Khorakoma” and “Anguzakoma” in Iran (1). It has been used in traditional medicine and as a spice in different foods in India and Nepal (1).

Recently, emphases are focused on the novel therapeutic agents from medicinal plants and many people prefer medicinal plants to chemical drugs (2). *F. assa-foetida* is a wild native plant in Iran and *F. asafoetida* gum extract has been used in Iranian traditional medicine for

abdominal pain, constipation and diarrhea treatment. It is also used for the treatment of asthma, influenza, stomachache, epilepsy, flatulence and intestinal parasites (3-5). Aphrodisiac, diuretic and sedative effects have been described for this plant (6). Several pharmacological effects including antiviral (7), antifungal (8), antioxidant (7), cancer chemoprevention (9), antispasmodic (10), hypotensive (10) and anti-diabetic (11) effects have been reported for *F. asafetida*.

Several fractions such as gum fraction (25%) and resin (40–64%, which contain ferulic acid esters (60%), free ferulic acid (1.3%), coumarin derivatives (e.g. umbelliferone), volatile oils (3%–17%) including sulphur-containing

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compounds (3,12) were isolated from plant. E-1-propyl sec-butyl disulfide, as the major component, and 25 other compounds were identified in the hydrodistilled oil of Iranian *Ferula assa-foetida* oil (13). E-1-propenyl sec-butyl disulfide (40.0%) and germacrene B (7.8%) are the major components of *Ferula assa-foetida*. Therefore, only two components constituted more than 70% of the oil using supercritical carbon dioxide under optimum conditions with extraction yield, based on hydrodistillation (13).

Umbelliprenin is a member of prenylated coumarins that present in *Ferula* species, which its chemoprevention activity on the cancer was reported (14). In addition, a concentration-dependent response of 25, 50, 100, 200, and 400 μ M umbelliprenin was decreased in DNA damage induced by H₂O₂ (15).

F. asafoetida is traditionally used for the treatment of asthma and angina pectoris (16), bronchitis, whooping cough and pneumonia in children (17-19). The observed relaxant effect of *F. asafoetida* on tracheal smooth muscle may indicate its bronchodilator effect (20).

Anticoagulant action of *Ferula asafoetida* gum extract has also been suggested (21). The beneficial effects of gum have been achieved from *Ferula asafoetida* in gastrointestinal and hemodynamic disorders (10). In addition, the relaxant effects of its gum extract on blood pressure were recorded from the anaesthetized rats (10). The present review summarizes the information regarding the relaxant effect of asafetida and its extracts on different smooth muscles and the possible mechanisms of this effect.

Methods

This review article was prepared by searching for the terms: *Ferula asafetida*, smooth muscles, umbelliprenin and relaxant effects. Information on *Ferula asafetida* was collected via search and studies in electronic databases including ISI Web of Knowledge, Medline/Pubmed, Scindirect, Embase, Scopus, Biological Abstracts, Chemical Abstracts and Google Scholar.

Results

The relaxant effect of various preparations of *Ferula asafetida* and its constituents on different types of smooth muscles were demonstrated which reviewed in the following sections:

Relaxant effects on tracheal smooth muscle

In previous studies, the relaxant effect of *F. assa-foetida* on smooth muscle of the tracheal chain (*in vitro*) was shown (20). Some constituents of the gum resin including carvacrol have inhibitory effect on muscarinic receptors of tracheal smooth muscle (22). In addition, we showed the relaxant effect of *F. asafoetida* extract by inhibitory effect for the plant on histamine (H₁) receptors of tracheal smooth muscles in the tracheal smooth muscle (23).

The *Ferula sinaica* (another species from *Ferula* genus) root extract also inhibited the contractions of rabbit tracheal and contractions of guinea pig tracheal smooth muscle induced by acetylcholine and histamine stimulation, respectively (24).

The relaxant effects of *F. asafoetida* and umbelliprenin on contracted smooth muscle by methacholine and KCl on the tracheal smooth muscle were also observed (25).

The relaxant effects of the extracts of *F. assa-foetida* and its constituents on tracheal smooth muscles are summarized in Table 1.

Relaxant effects on gastro-intestinal and urogenital smooth muscle

F. asafoetida gum extract reduces the spontaneous contraction of the isolated guinea-pig ileum (10). The inhibitory effects of *Ferula sinaica* (another species from *Ferula* genus) root extract on rabbit jejunum, guinea pig ileum, and guinea-pig uterine smooth muscle contractions by acetylcholine were also reported (24).

The spasmolytic and antispasmodic action of *F. assa-foetida* seed's essential oil against contractile induced by cumulative concentrations of acetylcholine were reported to be stronger than asafetida which might be due to the higher concentration of the constituents in the oil (26). The relaxant effect of the extracts of *F. assa-foetida* and its constituents on Gastro-intestinal and urogenital smooth muscle are summarized in Table 2.

Relaxant effects on vascular smooth muscle

The results of a study demonstrated that *F. asafoetida* gum extract (0.3-2.2 mg/100 g body weight) remarkably reduced the mean arterial blood pressure in anesthetized normotensive rats which at higher doses, the duration of the depressor response to extract was long-lasting (10). The

Table 1. Relaxant effect of the extracts and constituents of *F. assa-foetida* on tracheal smooth muscle

Extract, Constituent	Dose, Conce.	Method for Tissue smooth muscle contraction (TSM)	Response	Ref.
Aqueous extract	2, 5 and 10 mg/mL	KCl (60 mmol/L)	0.85, 5.13, 10.17	(25)
		Methacholine (10 μ mol/L)	31.6, 65.72, 91.07	(25)
Umbelliprenin	0.04, 0.2 and 0.4 mg/mL	KCl (60 mmol/L)	-2.42, -0.53, 8.97	(25)
		methacholine (10 μ mol/L)	8.59, 18.86, 26.28	(25)
Aqueous-ethanolic extract	2.5, 5, 10	Methacholine (range 0.1 - 1000 μ M)	97, 83, 80	(32)
Aqueous extract	2, 5 and 10 mg/ml	10 μ M methacholine \rightarrow preincubated tissues by propranolol and chlorpheniramine	34, 59, 80	(20)
		10 μ M methacholine \rightarrow preincubated tissues by propranolol,	42, 75, 100	(20)

Table 2. Relaxant effect of the extracts of *F. assa-foetida* and its constituents on gastro-intestinal and urogenital smooth muscle

Extract, Constituent	Dose, Conce.	Method for Tissue smooth muscle contraction (TSM)	Response	Ref.
Aqueous extract	1, 2, 3, 5 and 7 mg/ml	Spontaneous contractions	-83, 68, 54, 21, 9	(10)
		KCl (28 mM)	0, 3, 18, 23, 29	(10)
		Acetylcholine (25 µM)	3, 5, 20, 25, 29	(10)
		Histamine (25 µM)	4, 8, 32, 40, 53	(10)
Aqueous extract	0.1%, 0.2%, 0.3%	Acetylcholine (100 µM)	0, 50, 62	(26)
Essential oil	0.1%, 0.2%, 0.3%	Acetylcholine (100 µM)	20, 70, 85	(26)

inhibitory effects of *F. sinaica* root extract on contractions of rabbit aorta induced by norepinephrine stimulation were also observed (24).

The potent vasodilatation properties of *F. assa-foetida* extracts upon arterial rings were demonstrated (27). Kassis *et al.* demonstrated that the masculine property of this extract had mainly an endothelial-mediated effect and a secondary direct effect on arterial smooth muscle cells (27). In addition aphrodisiac effects of “masculine” extract at high doses were demonstrated by increase in penile erection episodes in the controlled rat studies. Similar effects of *Ferula hermonis* (related species) at a dose of 12 mg/kg in rats also were reported (28). The antioxidant and vasodilatation properties of masculine at concentrations of 0.05 and 0.2 mg/ml respectively were recorded (27).

Possible mechanisms of the relaxant effect of *Ferula asafoetida* on smooth muscles

The relaxant effect of the extract in smooth muscle might occurred by different mechanisms. For example, smooth muscle contractile tone can be relaxed by increased levels of adenosine 3,5-cyclic adenosine-monophosphate (cAMP) (29). In addition, one study showed that indomethacin (a cyclooxygenase inhibitor) remarkably inhibited the relaxant effect of *F. asafoetida* gum extract in isolated guinea-pig ileum which suggested that cyclooxygenase metabolites (e.g. prostaglandins such as PGE₂, PGD₂ and PGI₂) might be involved in this relaxation (10). Different possible mechanisms responsible for the relaxant effect of *F. asafoetida* on smooth muscles are reviewed in this section.

Calcium channel blocking effect

The relaxant effects of the *F. asafoetida* gum extract on tracheal, vascular, gastro-intestinal and urogenital smooth muscles have been suggested that, this natural product reduces the cytosolic Ca²⁺ in a non-specific manner. Ca²⁺ ions gain access to the cytoplasm through voltage-activated or receptor-operated calcium channels (30). KCl induced contraction by an increase in K⁺ and depolarization of smooth muscle fibers, leading to increased influx of calcium through L type voltage-operated channels (31).

The anti-cholinergic and anti-muscarinic effect of the plant

The inhibitory effect (antagonism effect) of extract on

muscarinic receptors was previously suggested (32). Acetylcholine induced contraction via M₃ subtype of muscarinic receptor in the muscle (33).

The inhibitory effect of acetylcholine on the existence and function of these muscarinic receptor subtypes was investigated in rabbit trachea in vitro on muscarinic system (34). The lower maximum response to methacholine has been revealed in experiments with high plant concentration indicating that non competitive antagonistic effect of the extract on muscarinic receptors (32).

Histaminic (H₁ receptor) antagonistic activity

Contraction induced by histamine which happens via H₁ receptor activation has been suggested (33). The relaxant effects of extract on isolated guinea-pig ileum preparations precontracted by histamine were higher than contraction induced by acetylcholine (10). The inhibitory effect of acetylcholine by histamine (H₁) receptors was suggested (35). In a previous study, the contribution of H₁ receptors inhibitory in incubated tracheal smooth muscle with chlorpheniramine was observed (23).

Stimulatory effect on β₂- adrenoceptors

The stimulatory effects of β agonists on β-adrenergic receptors in bronchi were suggested (36). In a previous study, the contribution of β-adrenergic receptors in incubated tracheal smooth muscle with propranolol (β-adrenergic receptors antagonist), the stimulatory effect of extract in β-adrenergic was observed (32).

Conclusion

F. asafoetida gum has been used in traditional medicine. The relaxant effects of *F. assa-foetida* and its essential oil on different types of smooth muscle on contracted tissues induced by various contractile agents have been shown. The different mechanisms of relaxant effects of *F. assa-foetida* including inhibitory effects of muscarinic receptors and histamine (H₁) receptors as well as β-adrenoceptors stimulatory effects on calcium channels have been reported.

Authors' contributions

Mohammad Reza Khazdair: Design of the study and preparation of the paper. Mohammad Hossein Boskabady: Help in design of the study and English editing of the paper.

Conflict of interests

There is no conflict of interest.

Founding/Support

None.

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