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

Mohammad Reza Khazdair¹, Mohammad Hossein Boskabady²*

¹Pharmaceutical Research Center and Department of Physiology School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
²Neurogenic Inflammation Research Centre and Department of Physiology, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

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**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:**

Asafoetida 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. asafoetida* 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.

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**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. asafoetida* 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. asafoetida*. 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...
Relaxant effects of Ferula assafoetida on smooth muscles

In previous studies, the relaxant effect of F. asafoetida on smooth muscle of the tracheal chain (in vitro) was shown (20). Some constituents of the gum resin including carvacoil 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. asafoetida 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. asafoetida seed's essential oil against contractile induced by cumulative concentrations of acetylcholine were reported to be stronger than asafoetida which might be due to the higher concentration of the constituents in the oil (26). The relaxant effect of the extracts of F. asafoetida 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-lasted (10). The

Table 1. Relaxant effect of the extracts and constituents of F. asafoetida on tracheal smooth muscle

<table>
<thead>
<tr>
<th>Extract, Constituent</th>
<th>Dose, Conc.</th>
<th>Method for Tissue smooth muscle contraction (TSM)</th>
<th>Response</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aqueous extract</td>
<td>2, 5 and 10 mg/mL</td>
<td>KCl (60 mmol/L) Methacholine (10 μmol/L)</td>
<td>0.85, 5.13, 10.17</td>
<td>(25)</td>
</tr>
<tr>
<td>Umbelliprenin</td>
<td>0.04, 0.2 and 0.4 mg/mL</td>
<td>KCl (60 mmol/L) Methacholine (10 μmol/L)</td>
<td>-2.42, -0.53, 8.97</td>
<td>(25)</td>
</tr>
<tr>
<td>Aqueous-ethanolic extract</td>
<td>2.5, 5, 10</td>
<td>Methacholine (range 0.1 - 1000 μM)</td>
<td>97, 83, 80</td>
<td>(32)</td>
</tr>
<tr>
<td>Aqueous extract</td>
<td>2, 5 and 10 mg/ml</td>
<td>10 μM methacholine → preincubated tissues by propranolol and chlorpheniramine</td>
<td>34, 59, 80</td>
<td>(20)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 μM methacholine → preincubated tissues by propranolol,</td>
<td>42, 75, 100</td>
<td>(20)</td>
</tr>
</tbody>
</table>
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 PGJ2) 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 Ca\(^{2+}\) in a non-specific manner. Ca\(^{2+}\) 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. asafoetida* 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.

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

<table>
<thead>
<tr>
<th>Extract, Constituent</th>
<th>Dose, Conc.</th>
<th>Method for Tissue smooth muscle contraction (TSM)</th>
<th>Response</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aqueous extract</td>
<td>1, 2, 3, 5 and 7 mg/ml</td>
<td>Spontaneous contractions</td>
<td>-83, 68, 54, 21, 9</td>
<td>(10)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KCl (28 mM)</td>
<td>0, 3, 18, 23, 29</td>
<td>(10)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acetylcholine (25 µM)</td>
<td>3, 5, 20, 25, 29</td>
<td>(10)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Histamine (25 µM)</td>
<td>4, 8, 32, 40, 53</td>
<td>(10)</td>
</tr>
<tr>
<td>Aqueous extract</td>
<td>0.1%, 0.2%, 0.3%</td>
<td>Acetylcholine (100 µM)</td>
<td>0, 50, 62</td>
<td>(26)</td>
</tr>
<tr>
<td>Essential oil</td>
<td>0.1%, 0.2%, 0.3%</td>
<td>Acetylcholine (100 µM)</td>
<td>20, 70, 85</td>
<td>(26)</td>
</tr>
</tbody>
</table>
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Conflict of interests
There is no conflict of interest.

Founding/Support
None.

References
30. Triggle DJ. Calcium ions and respiratory smooth