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Mohaddese Mahboubi
TabibDaru Pharmaceutical Company, Kashan, Iran

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REVIEW ARTICLE

The Beneficial Effects of *Ferula asafoetida* Oleo-gum Resin in Gastrointestinal Disorders

Mohaddese Mahboubi

Medicinal Plants Research Department, Research and Development, TabibDaru Pharmaceutical Company, Kashan, Iran

Abstract

Ferula asafoetida is a plant from Umbelliferae Family, which its gum is traditionally used to treat the gastrointestinal disorders (parasite, bloating, digestion, cancer). According to its traditional applications, the subject of this review was to evaluate the efficacy of *F. asafoetida* in management of different gastrointestinal disorders in modern medicine. For this purpose, the scientific resources (PubMed, Web of Science, Scopus, Google Scholar, SpringerLink, SciFinder, ACS Publications, and Wiley), traditional books, and thesis were investigated by the word of *F. asafoetida*, Hing, and gastrointestinal tract and the results were evaluated. There was one clinical trial on the efficacy of *F. asafoetida* in treatment of functional dyspepsia, and the other pharmacological activities such as anti-parasite, anti-cancer, anti-diarrhea and liver protective effects were evaluated in preclinical studies. Although, *F. asafoetida* can be proposed as a good candidate for treatment of gastrointestinal disorders, but the majority of studies have been limited to the experimental investigations. Therefore, evaluation of its efficacy and safety in well-designed human clinical studies is required to use of this valuable oleo-gum resin.

Keywords: *Ferula asafoetida*, Gum, Gastrointestinal diseases, Hing, Fetid

1. Introduction

Ferula asafoetida L. (Umbelliferae Family) with distinctive fetid smell is native to mountains of Iran, Pakistan, and Afghanistan and it is usually exported from Iran to other parts of the world, especially to India. The English common name of *asafoetida* is the “Food of the Gods”, or “Devils dung”.

Asafoetida is a two syllabubs Latin word (Assafoetida) with the means of stinky gum [1]. Oleo-gum resin of *F. asafoetida* is extracted from its root and contains the essential oil (6–17%), resin (40–64%), and gum (20–25%) [2]. Yellowish-white to reddish brown color *asafoetida* gum has intense alliaceous penetrating odor; and bitter, alliaceous and acrid taste. Carbohydrates (67.8%), moisture (16%), protein (4%), fat (1.1%), minerals (7.0%) and fibers (4.1%) are present in *asafoetida* gum [3]. Umbelliferone (7-hydroxycoumarin), karatavicinol, umbelliprenin, farnesiferol B, and farnesiferol C are extracted from *F. asafoetida* gum [4]. The yield of

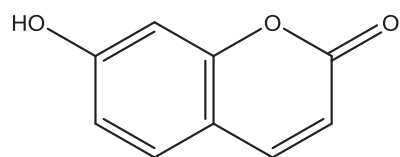
resin and its chemical profile influences by different factors including the climatic, genetic and edaphic factors. There is a positive correlation between precipitation rate and the yield of resin from the roots. The high temperature (low altitude and precipitation rate) increases progressively the essential oil's yields [5]. The main industrial compound from *asafoetida* is its oleo-gum resin, which it is rich in essential oil [6]. (E)- β -ocimene, n-propyl sec-butyl disulfide, (Z)-propenyl sec-butyl disulfide, (E)-propenyl sec-butyl disulfide, α -pinene, and β -pinene are the main components of *asafoetida* essential oil [7] (Fig. 1).

Asafoetida gum is used as condiment and flavor in Indian food culture. In Nepal, *asafoetida* is used as a part of daily diet [8]. A combination of *asafoetida* and pine nuts is used to flavor the foods. *Asafoetida* is traditionally used as digestive aid, appetizer, and for treatment of flatulence, colic, worms (round worms, pinworms) and other intestinal disorders [9]. Frying the *asafoetida* gum in oil or blending with

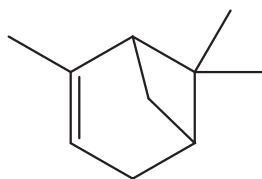
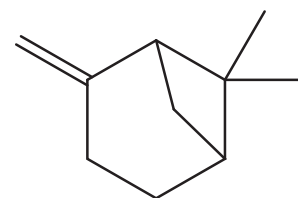
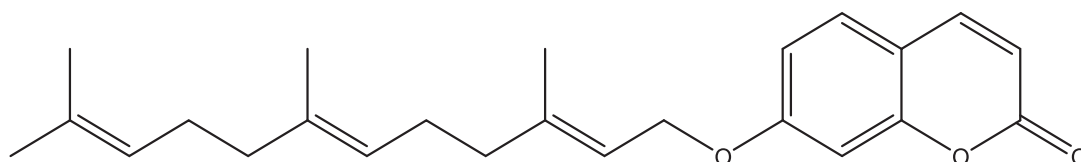
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E-mail address: mahboubi1357@yahoo.com.

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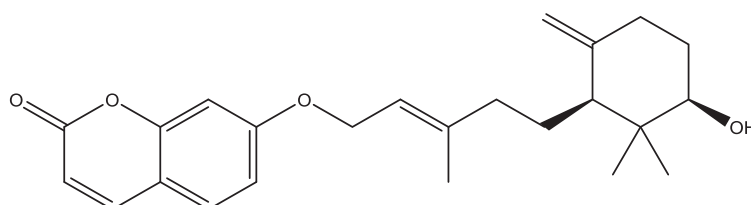
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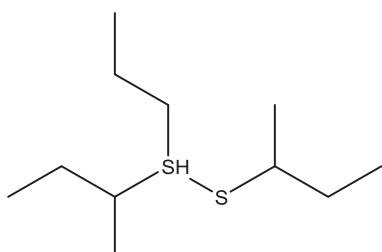
Umbelliferone (MW: 162.14)

 α -pinene (MW: 136.24) β -pinene (MW: 136.238)

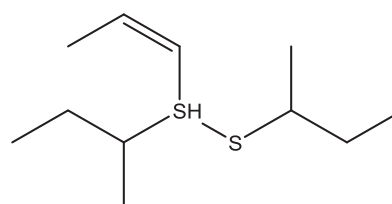
Umbelliprenin (MW: 366.5)



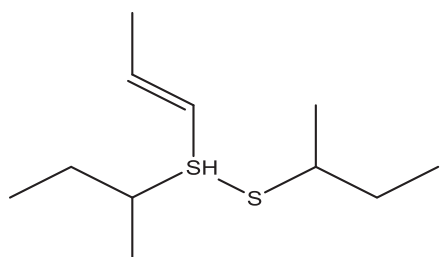
Farnesiferol B (MW: 382.5)



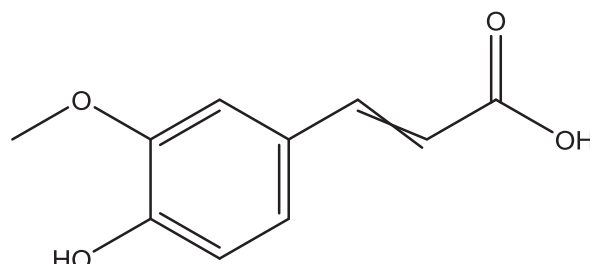
n-propyl sec-butyl disulfide (MW: 164.332)



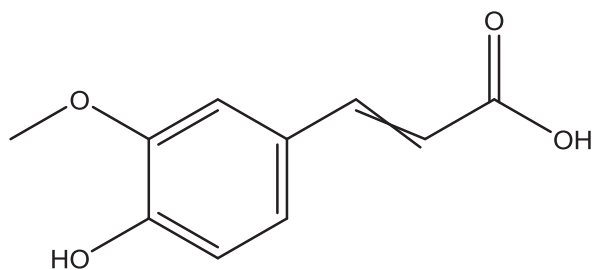
(Z)-propenyl sec-butyl disulfide (MW: 162.3)



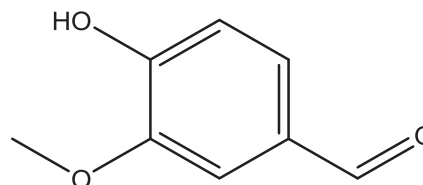
(E)-propenyl sec-butyl disulfide (MW: 162.3)



ferulic acid (MW: 194.18)



ferulic acid (MW: 194.18)



Vanillin (MW: 152.15)

Fig. 1. The structure of components in asafetida oleo gum resin.

flour and maize reduces its harshness [10]. The same quantity of asafoetida herb with opium was ingested as opium's antidote. Asafoetida gum is used as necklace against cold and fevers [11]. Oral use of asafoetida is prescribed for enhancing the libido, male fertility and erectile dysfunction in Greco-Arab Traditional medicine [12]. Intra-vaginal asafoetida gum is used as contraceptive agent in Egypt [13]. In India, dried asafoetida gum, with *Brassica alba*, and rocky salt in vinegar is taken orally as abortifacient [14]. In Afghanistan, asafoetida gum hot water suspension is used for whooping cough, hysteria, and ulcers [15]. Topical application of asafoetida paste on chest is used for whooping cough in Fiji [16].

There are some review articles on biological activities of asafoetida [6,17,18], but there is no review study for its efficacy in gastrointestinal disorders. Due to traditional uses of asafoetida in gastrointestinal disorders, and no presence of review on its efficacy in gastro-intestinal disorders, the aim of this article was to evaluate the modern literatures on efficacy of asafoetida in gastrointestinal disorders according to its traditional claims.

2. Traditional uses of *F. asafoetida* in gastrointestinal diseases

Asafoetida is known as anti-colic herb, which prevents the intestinal spasms and spasmodic pain [10]. The indication of asafoetida in European countries is abdomen cancer, liver cancer, cholera, colic (cramp, flatulence), colitis, constipation, diarrhea, dyspepsia, stomachache, and worm [1]. Asafoetida dried fruit is the ingredient of gruel or pills for treatment of constipation, indigestion, dyspepsia, chronic gastritis, and irritable colon in western countries [19]. Asafoetida is used for colic pain, indigestion, flatulence, and constipation in Unani, Arab, and Ayurveda traditional medicines [20]. Asafoetida gum is used in formulations of Hingavaadi Bati, Hingu-triguna Taila (Ashtaanga Hridaya), Habb-e-Hilteet for treatment of colic, loss of appetite, intestinal colic, flatulence, and chronic constipation. In India, the combination of asafoetida with cayenne, pepper and sweet flag is a remedy for cholera [21]. Asafoetida is known as anti-helminthic gum, and is used for treatment of ascites, and dysentery in Taiwan [22]. In China, plant decoction is vermifuge herb [23]. Oral administration of asafoetida dried root is known as vermifuge, analgesic and antispasmodic agent in Egypt [24]. Oral asafoetida gum hot water suspension is used for upset stomach

[16]. Asafoetida gum resin is taken orally to prevent the guinea worm diseases [25]. In Nepal, asafoetida gum water extract is used for its anti-helminthic properties [26]. In United States, asafoetida gum fluid extract is taken orally as anti-helminthic and powerful antispasmodic agent [27]. In Iranian traditional medicine, asafoetida is used for treatment of gastrointestinal ailments (spasm, constipation), intestinal parasites, stomach tonic, and dyspepsia (indigestion, appetite, bloating). Avicenna used asafoetida for digestion [28]. Due to traditional uses of asafoetida gum in treatment of gastrointestinal diseases, we evaluated its efficacy in modern medicines (Tables 1 and 2).

2.1. *F. asafoetida* and liver functions

Liver is a vital organ for detoxification of the body and the responsible organ for metabolic functions. The liver protective effects of oral 100 mg/kg asafoetida aqueous extract against 3 mg/kg sodium arsenate for 4 weeks in Swiss albino mice against sodium arsenate reduced the alanine aminotransferase level (ALT) from 210 ± 7.26 U/ml to 108 ± 2.71 and 82.0 ± 1.24 U/ml after 4 and 6 weeks of asafoetida administration. The aspartate aminotransferase (AST) level reduced from 198 ± 4.78 to 112 ± 1.93 U/ml and 78 ± 1.07 U/ml after 4 and 6 weeks of asafoetida administration. Asafoetida extract reduced the increased alkaline phosphatase (ALP) level in arsenic treated mice (24 ± 1.91 KA) to 17 ± 0.85 and 13 ± 0.51 after 4 weeks and 6 weeks. Bilirubin level reduced from 2.43 ± 0.48 mg/dl to 1.67 ± 0.08 mg/dl and 1.30 ± 0.03 mg/dl after 4 and 6 weeks of treatment with asafoetida [29]. The elevation in ALT, AST, ALP, and bilirubin levels in presence of arsenic is a feature of abnormal liver function, which is associated with high incidence of liver and cardiovascular diseases [30]. Therefore, oral administration of asafoetida significantly restored the liver enzymes in arsenic exposed animals, which may be caused by the components of asaresinotannols A, asaresinotannols B, ferulic acid, and umbelliferone [3].

The liver protective effects of asafoetida aqueous extract (50, 100, 200 mg/kg) were compared with 1 ml/kg/day Liv-52 against 1 ml/kg carbon tetrachloride (CCL₄) for a period of 14 days in albino rats. The treatment duration was 21 days after inducing the hepatotoxicity. CCL₄ significantly increased the level of ALT, AST, and total bilirubin contents. Treatment of animals with different concentrations of asafoetida significantly reduced the serum ALT,

Table 1. The Potency of *asafoetida* in gastrointestinal diseases.

Biological Activity	Asafoetida	Model	Against	Duration	Results	Ref
Liver protective	Gum aqueous extract (100 mg/kg)	Swiss albino mice	sodium arsenate	4 and 6 weeks	↓ALT ↓AST ↓ALP ↓Bilirubin	[29]
	Gum aqueous extract (50, 100, 200 mg/kg)	albino rats	1 ml/kg carbon tetrachloride (CCL ₄)	21 days after inducing the hepatotoxicity	↓ALT ↓AST ↓bilirubin ↑SOD ↓lipid peroxidation ↓body weights ↓abdominal fats ↓dense of lipid droplets ↓size of abdominal ↓leptin level	[31]
	Gum water suspension (25, 50 mg/kg)	Rats	10% fresh fructose	eight weeks	↓lipid peroxidation ↓body weights ↓abdominal fats ↓dense of lipid droplets ↓size of abdominal ↓leptin level	[33]
Functional dyspepsia	Gum Powder (500 mg) or placebo	48 patients with functional dyspepsia (25–60 years old)	Patients with Functional DYSPEPSIA	30 days	↓GSRs ↓GDSS ↓NDI ↓bloating ↓postprandial fullness ↓appetite ↓motion sickness ↓Indigestion Safe treatment	[36]
Anti-ulcer	Gum aqueous extract (25, 50 mg/kg)	mice	48 mg/kg indomethacin	4 days	↓ulcer index, ↑curative ratio ↓inflammation around the central vein	[38]
Anti-secretory and anti-ulcer	Gum aqueous suspension (250, 500 mg/kg)	Wistar albino rats	pylorus ligated (Shay) test	–	↓ basal gastric secretion inhibition of ulceration, inflammation, dysplastic and necrosis of gastric mucosa ↑ gastric wall mucus ↑ gastric mucosal NP-SH	[20]
Analgesic anti-inflammatory	Gum water extract 2.5, 5, 10, and 20 mg/kg	male albino mice	hot plate test and acetic acid writhing test	–	↓Pain ↓carrageenan induced edema.	[45]
Antispasm	Gum Aqueous extract, essential oils (0.1, 0.2, and 0.3%)	–	ileum segments	20 minutes	↑ antispasmodic effects of oil than aqueous extract ↓ maximum contraction induced by acetyl choline	[48]
Antidiarrheal	Gum ethanol extract (100, 200 mg/kg)	Wistar adult male rats	–	1.5 hours	↓ movement of intestinal materials inhibition of materials transit ↓ progression of gastrointestinal passage	[56]

(continued on next page)

Table 1. (continued)

Biological Activity	Asafoetida	Model	Against	Duration	Results	Ref
Antidiarrheal	Gum ethanol extract (400 mg/kg)	Wistar adult male rats	–	1.5 hours	↑ path of material in intestine ↓ diarrhea score ↓ changes in stool weight	[56]
Anti-helminthic	Gum essential oil, powder vs. Clotrimazol	<i>Blastocystis</i> sp. Subtype 3	–	–	↓ count irreversible damages and detrimental changes in morphology ↑ anti-helminthic effect of asafoetida than piperazine citrate	[59]
Anti-helminthic	Gum aqueous extract (25, 50, 100 mg/ml) vs. Piperazine citrate	<i>Pheretima postuma</i>	–	–	↑ anti-helminthic effect of asafoetida than piperazine citrate	[60]
Anti-helminthic	aerial parts ethanol extract (100, 50, 10, mg/ml)	<i>Strongylus</i> spp.	–	–	killed 100% larvae after 48 hours incubation	[61]
Anti-Cancer Effects	Gum asafoetida (50, 100, 200 mg/kg)	Sprague Dawley rats	MTT assay	16 weeks	↑ body weight ↓ Tumor incidence ↓ tumor multiplicity ↓ tumor size ↓ TSA	[65]

AST and bilirubin content. The effects of 200 mg/kg asafoetida extract on ALT, AST and total bilirubin content were higher than the other doses of *F. asafoetida* gum. CCL₄ significantly reduced the level of Super Oxide Desmutase (SOD), which is associated with increase in lipid peroxidation. Treatment of animals with asafoetida extracts significantly elevated the level of SOD and reduced the lipid peroxidation [31]. Increase in liver enzymes by CCL₄ is associated with liver damages. The strong antioxidant activity of SOD and lowering the oxidative stress in the liver play an important role in liver protective effects of asafoetida gum extract. Asafoetida and its sulfide components exhibited the strong antioxidant activity against produced free radicals [32], which restored the activity of antioxidant enzymes, and liver enzymes and protected against the toxic effects of CCL₄ on liver.

The anti-diabetic effects of Asafoetida gum water suspension (25, 50 mg/kg) were evaluated against 10% fresh fructose treated rats for eight weeks. The body weight, liver weight, abdominal fat, liver fat, leptin level and the histopathology of epididymis of rats were determined. A significant increase in fasting blood sugar (FBS) ($p < 0.05$) and IPGT (intra-peritoneal glucose tolerance Tests) ($p < 0.01$) was observed in control group. Assessment the body weights in different groups, every two weeks exhibited that asafoetida gum water suspension significantly reduced the body weights and abdominal fats in comparison with control group. Asafoetida gum water suspension significantly reduced the dense of lipid droplets and the size of abdominal adipocytes in histopathology smears of treated rats ($p < 0.05$). The leptin level was significantly lower in asafoetida group than that of control group [33]. Asafoetida inhibited the α -glucosidase enzyme and reduced the glucose absorption from digestive system and blood glucose [34]. Hydrolysis of asafoetida proteins by gastric digestive enzymes enhanced the reducing power activities of asafoetida gums [35]. According to the results of this study [33], asafoetida gum water suspension reduced the body and liver fats in type 2 diabetic rats. High level of leptin in serum was associated with the fat deposition and increase in body weight. Asafoetida water suspension significantly reduced the hepatosteatosis (Fatty liver disease) in obese type 2 diabetic rats and showed anti-obesity effects in rat animal model and protected the liver against hepatosteatosis by

Table 2. The identified components responsible for biological activity in gastrointestinal tract.

Asaresinotannol-A Asaresinotannol-B Ferulic acid Umbelliferone	Antioxidant activity	Liver protective effects	[3]
Sulfide components Flavonoids Glycosides Ferulic acid Coumarins	Antioxidant activity antioxidant activity membrane stabilizing agent non-competitive antagonistic effects on muscarinic receptors	Liver protective effects anti-ulcer effects	[32] [39] [40–42] [44] [43]
Galbanic acid Ferulin Umbelloprenin Ferulic acid Fetidone A Fetidone B	blocks the farnesyltransferase inhibitory effects against lipoxygenase	anti-secretory effects Analgesic, anti-inflammatory effects	[4] [46]
Sesquiterpene Hydrocarbons Monoterpene Hydrocarbons oxygenated sesquiterpenes	reduced the maximum contraction induced by acetyl choline	relaxant effects of asafoetida on isolated ileum	[48]
Pinenes Thymol	competitive effects on muscarinic receptors activates the adrenergic receptors on calcium channels	relaxant effects	[54,55] [44,53] [49,78]
Ferulic acid Galbanic acid Vinyl disulfides	induces the apoptosis in cancerous cell lines via activation of caspase and inhibition of Mcl-1 activated the TRPA1	chemo protective effects	[66] [67] [69] [68]

reducing the serum leptin level. Asafoetida by reduction of leptin level, the lipid droplets and the size of abdominal adipocytes is suitable candidate for obesity and other metabolic diseases related to obesity.

2.2. *F. asafoetida* and functional dyspepsia

One of the most common diseases related to gastrointestinal tract is functional dyspepsia, which is associated with bloating, belching, heart burn, indigestion, epigastric pain, early satiety and poor quality of life.

In a double blinded placebo controlled randomized study, the efficacy of asafoetida gum was evaluated on 48 patients with functional dyspepsia (25–60 years old), who diagnosed by Rome III diagnostic criteria. The patients were randomly divided in two groups of asafoetida and placebo groups and the patients received 2 capsules of 250 mg asafoetida or placebo for 30 days. The efficacy of treatments, adverse effects, hematological and pathological parameters was evaluated in two groups of treatments. The individual dyspepsia symptoms, overall severity scores were compared between two groups. In regard of Gastrointestinal Symptom Rating Scale

(GSRS), asafoetida capsule significantly reduced the overall severity score to 51.6% in comparison with placebo and baseline. The Glasgow Dyspepsia Severity Score (GDSS) significantly reduced from 10.45 ± 0.21 to 4.80 ± 0.17 ; ($p \leq 0.001$) in *F. asafoetida* group and from 10.79 ± 0.20 to 9.22 ± 0.25 ; ($p > 0.05$) in placebo group. A significant improvement in functional dyspepsia symptoms was reported in 69% of patients in asafoetida group, and 87% of patients in this group had no treatment with synthetic drugs. Nepean Dyspepsia Index-Short Form (NDI-SF) showed 38.67% reduction in overall symptoms in asafoetida group, compared with placebo group. 81% of the subjects had significant reduction in clinical symptoms of GSRS, GDSS, and NDI. Asafoetida significantly reduced bloating (58%), postprandial fullness (74%), appetite (69%), motion sickness (75%), and indigestion (77%). 66% of patients in asafoetida group were symptom free. Asafoetida capsule had no significant effect on hemoglobin, RBC, PCV, MCV, MCH, MCHC, liver and renal markers in comparison with placebo group [36]. The efficacy of asafoetida in treatment of functional dyspepsia can be related to its some biological activities such as its anti-secretory, analgesic, anti-inflammatory, antioxidant and relaxant effects on gastro-intestinal effects.

2.3. The anti-secretory and anti-ulcer effects of *F. asafoetida*

The use of anti-secretory drugs in patients with functional dyspepsia can reduce the clinical symptoms of disease [37].

The anti-secretory effects of intra-peritoneal injection of 250, 500 mg/kg body weight *asafoetida* aqueous suspension were determined in Wistar albino rats by pylorus ligated (Shay) test. The stomach of animals was removed 6 hours after surgery and the anti-secretory and anti-ulcer effects of *asafoetida* water suspension were determined. The titration of stomach content by NaOH exhibited that *asafoetida* water suspension significantly reduced basal gastric secretion and completely inhibited the ulceration. *Asafoetida* water suspension reduced the basal gastric secretion from 8.83 ± 0.98 ml to 6.08 ± 0.15 (250 mg/kg) in control group and 4 ± 0.22 ml (500 mg/kg) in *asafoetida* water suspension treated group. The ulcer index in control group was 1.0 ± 0.36 , while ulcer index was completely inhibited in *asafoetida* water suspension. The pretreatment of mice with *asafoetida* water suspension, 30 minutes before oral administration of indomethacin (30 mg/kg b.w) in fasted rats, inhibited the ulceration at the concentration of 500 mg/kg (20.66 ± 4.05). *Asafoetida* aqueous extract (250 mg/kg) reduced the ulcer index in indomethacin treated rats (24.66 ± 4.05), but the difference was no significant with control group (34.66 ± 4.58). Pretreatment of rats with *asafoetida* water suspension (250, 500 mg/kg) increased the gastric wall mucus from 351.30 ± 15.76 , and 367.81 ± 11.14 to 327.07 ± 9.07 , and 464.31 ± 12.92 in control and ethanol treated groups. Also, pretreatment of rats with *asafoetida* water suspension in presence of necrotizing agent significantly reduced the stomach lesions. The gastric mucosal NP-SH (non-protein sulfhydryl groups in glandular stomachs of mice) was evaluated in ethanol (80%) treated fasted rats and *F. asafoetida* water suspension groups. Ethanol (80%) significantly reduced the NP-SH in ethanol treated rats (6.38 ± 0.33 $\mu\text{mol}/100$ mg), while pretreatment of rats with *asafoetida* water suspension (250, 500 mg/kg) inhibited the depletion of NP-SH (6.47 ± 0.36 ; 7.94 ± 0.80 $\mu\text{mol}/100$ mg). The NP-SH concentration was 8.59 ± 0.33 $\mu\text{mol}/100$ mg in control group. Hemorrhage, ulceration, inflammation, dysplastic and necrosis of gastric mucosa were inhibited in ethanol treated animals. Congestion, edema, and erosion were seen in *F. asafoetida* water suspension group as ethanol treated group [20].

The anti-gastric ulcer effects of *asafoetida* aqueous extract was evaluated in mice by oral single dose of

48 mg/kg indomethacin. The animals were divided in four groups of control group (5 ml/kg saline solution), indomethacin group, and oral single dose of 25, 50 mg/kg *asafoetida* for 4 days. The lesions in liver and stomach were determined in different groups, and the ulcer index was determined by sum of total length long ulcers and pectorial lesions, and the maximum percent of curative ratio were recorded. Pretreatment of mice with *asafoetida* significantly reduced the ulcer index, which was associated with microscopic and macroscopic curative ratio in comparison with indomethacin group. The ulcer healing process was dose dependent. The percent of microscopic ulcer protections were 80.3% and 89.2% in different doses of 25 and 50 mg/kg *asafoetida* groups, while the corresponding macroscopic protections were 59.1% and 73.5% in *asafoetida* groups. The macroscopic and microscopic ulcer indexes were 13.2, and 11 in indomethacin treated group, while the microscopic ulcer indexes reduced to 3.2 and 2.1 in *asafoetida* groups. Histopathology of gastric mucosa in control group had normal structure, while deep damages in mucosal structures and gastric glands were observed in indomethacin group. A mild discontinuity of mucosal layers and local edema in stomach gland were seen in low dose of *asafoetida* group, the structure of mucosal layers with less disruption and edema and ulcer were seen in this group. The results of histopathology experiments showed the cytoprotective effects of *asafoetida* extract in a dose dependent manner. *Asafoetida* aqueous extract reduced the inflammation around the central vein, and it dilated the hepatic sinusoids, and expanded the vessel in portal area [38]. *Asafoetida* water suspension significantly inhibited the basal gastric acid secretion and ulceration in pylorus ligated rat animal model and showed inhibitory effects against indomethacin induced mucosal injury or injuries by other necrotizing agents. *Asafoetida* water suspension significantly increased the gastric wall mucus in rats. The presence of flavonoid glycosides, ferulic acid and coumarins in *asafoetida* water suspension [39] as antioxidant compounds and membrane stabilizing agent scavenge the free radicals in membranes [40–42]. The antioxidant activity *asafoetida* plays an important role in anti-ulcer effects of *asafoetida* gum. The strong cell defense of *asafoetida* gum protect the cell membrane, which may involve in its anti-ulcer effects [43]. The non-competitive antagonistic effects of *asafoetida* on muscarinic receptors could be one of proposed mechanism(s) of action [44]. Galbanic acid blocks the farnesyl transferase. Farnesyl transferase, as critical enzyme activates the oncogene process in

the body [4]. Therefore, the anti-secretory effects of asafoetida and its inhibitory effects on ulceration and mucosal injuries help the patients with functional dyspepsia.

2.4. The analgesic effects of *F. asafoetida*

Pain is one feature of gastrointestinal diseases like functional dyspepsia and IBS. The analgesic effects of asafoetida have been confirmed in different studies. The anti-nociceptive effects of asafoetida gum aqueous extract (2.5, 5, 10, and 20 mg/kg) was evaluated in hot plate test and acetic acid writhing test in male albino mice. For evaluation of some possible mechanisms related to its anti-nociceptive effects, naloxone (5 mg/kg), theophylline (5 mg/kg), yohimbine (5 mg/kg), methysergide (5 mg/kg), haloperidol (1 mg/kg), and glibenclamide (2 mg/kg) were applied 30 minutes before intra-peritoneal administration of 10 mg/kg asafoetida. The carrageenan induced edema inhibition was evaluated by intra-peritoneal administration of asafoetida, 15 minutes before injection of carrageenan. The soybean 15-lipoxygenase assay was used and lipoxygenase inhibition and the antioxidant activity were determined by DPPH assay. In hot plate test, the maximum analgesic effects were observed 15 minutes after injection of 10 mg/kg asafoetida. In acetic acid writhing test, the effect of 10 mg/kg asafoetida was significantly lower than control group. The anti-nociceptive effects of asafoetida were not reversed by naloxone, glibenclamide, theophylline, yohimbine, methysergide, and haloperidol. Asafoetida (2.5 mg/kg) had significant anti-inflammatory effects in carrageenan induced mice paw edema. Asafoetida gum extract inhibited the lipooxygenase and had antioxidant activity. The analgesic effects of 10 mg/kg asafoetida aqueous extract was higher than 8 mg/kg morphine sulfate in hot plate test and acetic acid induced writhing test [45]. It seems that the anti-nociceptive effects of asafoetida gum extract was not mediated by the receptor antagonizing agents such as naloxone and other antagonists, and the inhibition of lipooxygenase/cyclooxygenase in arachidonic cascade implied on its central and peripheral analgesic effects. The analgesic effects of asafoetida are attributed to ferulin. The anti-inflammatory effects of asafoetida can be related to umbelloprenin, ferulic acid, fetidones A, B with inhibitory effects against lipoxygenase [46].

2.5. Relaxant effects of *F. asafoetida*

Muscle relaxants can improve the gastric accommodation in functional dyspepsia, but Gastroparesis

(delayed gastric emptying) needs the prokinetics to accelerate the gastric stasis.

Asafoetida (400 mg/kg) inhibited the intestinal propulsion and reduced the propulsive action of intestine in mice and exhibited the spasmolytic effects [47]. The antispasmodic and spasmolytic actions of asafoetida aqueous extract and essential oils (0.1, 0.2, and 0.3%) were evaluated on segments of ileum for 20 minutes. The contractile response of each treatment was induced by 10^{-12} – 10^{-2} acetylcholine. The spasmolytic evaluations were determined by treatment of tissue with 10^{-4} acetylcholine for 5 minutes, and then the maximum contractions were determined. The antispasmodic effects of asafoetida oil were stronger than its gum aqueous extract. Asafoetida (0.2% and 0.3%) reduced the maximum contraction induced by 10^{-4} acetylcholine by 12% and 43% [48]. The amount of sulfur compounds in asafoetida oleo-gum resin was higher than its essential oil. The relaxant effects of asafoetida on isolated ileum was dose dependent, while the amounts of sesquiterpene hydrocarbons, monoterpene hydrocarbons, and oxygenated sesquiterpenes were higher in asafoetida seed essential oil [48].

Asafoetida can inhibit the histamine induced smooth muscle contractions of gastrointestinal tract [49]. There are different mechanisms are supposed to be related to the relaxant effects of asafoetida gum extracts. Asafoetida gum extract nonspecifically reduces the cytosolic Ca^{2+} , which has access to the cytoplasm through L-type voltage operated channels. The vasodilatory effects of asafoetida essential oil is mediated by activation of potassium channels, inhibition of calcium channels and intracellular calcium mobilization [50]. Rather than its calcium channel blocking effects, the inhibitory effects of asafoetida extract on muscle's M_3 subtype muscarinic receptors or its histaminic antagonistic activities, or stimulatory effects on β -adrenergic receptors are other related mechanisms of action in relaxant effects of asafoetida on smooth muscle [51]. Asafoetida inhibits the muscarinic and histaminic (H_1) receptors or activates the adrenergic receptors on calcium channels [44,51–53]. The relaxant effects of *asafoetida* extract is attributed to pinenes [54,55], thymol and their competitive effects on muscarinic receptors in presence of atropine [44,53]. Atropine in presence of *F. asafoetida* has more inhibitory effects on smooth muscles.

2.6. Anti-diarrhea effect of *F. asafoetida*

Diarrhea can be a clinical sign of some gastrointestinal diseases, which is associated with loose,

watery stools, abdominal cramps, pain, and bloating.

The anti-diarrheal effect of asafetida ethanol extract (90%) was evaluated in Wistar adult male rats. The LD₅₀ of asafetida ethanol extract was determined at doses of 10, 100, 1000, 1600, 2900, 5000 mg/kg for 14 days. The LD₅₀ was determined and 0.1 of LD₅₀ was used as therapeutic dose. In this experimental study, rats were randomly allocated into negative control (Normal Saline), positive control (0.1 mg/kg atropine) and interventional groups (100, 200, 400 mg/kg). 1.5 hours after treatment of groups, the animal received the oral active charcoal (1.5 ml – 10%) plus 5% tragacanth and the time of intestinal passage of materials was determined. Atropine as anti-cholinergic drug significantly reduced the intestine movements ($p < 0.05$). The path of material in intestine insignificantly was higher in 400 mg/kg asafetida group than that of control group. 100 and 200 mg/kg asafetida significantly reduced the movement of intestinal materials, and the low doses of asafetida had higher effects on intestinal transit. Among different doses of asafetida, only 100 mg/kg asafetida significantly inhibited the transit of materials ($p < 0.05$). Progression of gastrointestinal passage was 89.16 ± 3.45 cm in control group, while in atropine group (0.1 mg/kg) was 52.86 ± 7.24 cm. The progressions of gastrointestinal passage were 97 ± 1.15 , 65.88 ± 8.69 , and 62.23 ± 0.67 cm for 400, 200, and 100 mg/kg asafetida extract, respectively. The use of 0.1 mg/kg atropine, and 100 mg/kg asafetida reduced the progression of gastrointestinal passage to 46.45 ± 2.42 cm. 100 mg/kg asafetida extract had no significant difference with atropine in progression of gastrointestinal passage ($p < 0.05$).

The effect of asafetida (100, 200, 400 mg/kg) was compared with loperamide (3 mg/kg) on castor oil induced diarrhea in rats. One hour after treatments, all animals received 2 ml castor oil and each rat was kept in cages, separately. The variables were including the time of starting the diarrhea, diarrhea scores, the number of stools, the stool weights during 4 hours. Loperamide inhibited the diarrhea during four hours. In asafetida group, the time for start of diarrhea insignificantly increased by increase in dose of asafetida. The diarrhea score and changes in stool weight significantly reduced in asafetida (400 mg/kg) in comparison with control group ($p < 0.05$), although an insignificant reduction in stool weight was observed in other groups.

For evaluating the effects of asafetida hydro-alcoholic extract on liquid accumulations in

experimental diarrhea model, all animals received the castor oil and active charcoals, 0.5 hours after that, the small intestine length, and the whole way by active charcoal, and the secreted liquids into intestines were evaluated. Assessing the amount of accumulated liquid in intestine after induction of diarrhea showed that asafetida gum reduced the secretion and accumulation of liquids in intestine, but these reductions were insignificant. Loperamide significantly inhibited the progression of intestinal materials, while asafetida gum insignificantly reduced the intestine movement [56]. The results of this study showed asafetida ethanol extract at low doses (100 mg/kg) had inhibitory effects on transit of intestinal materials, which is in agreement with researchers who reported its spasmolytic effects on guinea pig ileum [49,57] and high doses of asafetida significantly increased the intestinal movement, which it makes suitable for constipation, paralysis, reduced intestinal movement after surgery.

2.7. Anti-parasite effects of *F. asafetida*

Asafetida is traditionally used for its anti-helminthics properties in Iran, China and Nepal [58]. *Blastocystis hominis* is the most common intestinal parasite in human, which infects 10% of people in developed countries, and 50–60% in developing countries. Clotrimazole is recommended for treatment of this parasite, but its application is associated with adverse effects. Asafetida essential oil decreased the count of different isolates of *Blastocystis* sp. Subtype 3, in a dose and time dependent manner. Asafetida powder and its essential oil had different inhibitory effects on *Blastocystis* sp. Subtype 3. Asafetida powder and essential oil caused irreversible damages on *Blastocystis* sp. Asafetida powder (16 and 20 mg/ml) had the maximum inhibitory effects on *Blastocystis* sp. with inhibition percent of 97.3–100%. Asafetida essential oil (40, 50 mg/ml) had the highest percentage inhibition about 84–100%, and 100%, respectively. *Blastocystis* morphology had detrimental changes in presence of higher concentrations of *Blastocystis* sp., and viable vacuolar forms were replaced by granular forms with shriveled appearance. So, the disintegrated parasites, and cell debris were seen under the microscope observations. The minimal inhibitory concentration (MIC) of asafetida powder and oil were 16 and 40 mg/ml, respectively, and these MIC values killed the *Blastocystis* sp. after 72 and 144 hours, respectively. Clotrimazole at the concentration of 10, 100, and 500 $\mu\text{g/ml}$ completely inhibited the growth of *Blastocystis* sp. *in vitro* condition [59].

The anti-helminthics effect of asafotida aqueous extract (25, 50, 100 mg/ml) was evaluated against *Pheretima postuma* was compared with Piperazine citrate. The paralysis time for *P. postuma* (min) at concentrations of 25, 50, 100 mg/ml asafotida aqueous extract were 24 ± 0.14 , 17 ± 0.13 , and 6 ± 0.1 and the time for death at these concentrations were 56 ± 0.17 , 39 ± 0.15 , and 18 ± 0.04 min. Piperazine citrate (25, 50, and 100 mg/ml) lysed the *P. postuma* at 22 ± 0.08 , 15 ± 0.15 , and 8.0 ± 0.06 min, the corresponding time for death were 52 ± 0.13 , 37 ± 0.18 , and 20 ± 0.02 min. So, asafotida aqueous extract (100 mg/ml) had the best effect on killing the worm. The anti-helminthic effect of asafotida gum aqueous extract was higher than piperazine citrate [60].

Strongylus spp. is an important nematode parasite of horses and related equidae. 1 ml asafotida aerial parts ethanol extract (100, 50, 10, mg/ml) were treated with 1 ml of *Strongylus* spp. larval suspensions and the survival rates of larvae were determined 1, 2, 3, 24, and 48 hours after incubation at 25 °C. The hydro alcoholic extract of asafotida killed over than 90% of the larvae on the first day of incubation. 50 and 100 mg/ml asafotida extract killed 100% larvae after 48 hours incubation [61].

The results of anti-parasite effects of asafotida have been confirmed in experimental studies, and require its evaluation in pharmacological and human studies.

2.8. *F. asafotida* and cancer

Gastrointestinal cancers are a group of cancers in esophagus, stomach, pancreas, colon, rectum, biliary system, liver, and small intestines. The indication of *F. asafotida* in European countries is abdomen, and liver cancers [1].

The cytotoxic effects of asafotida essential oil on human liver carcinoma cell lines (HCC) by MTT assay were in a dose dependent manner. The IC_{50} for essential oil were 7.21 ± 0.29 μ g/ml and 8.0 ± 0.36 μ g/ml for HepG2 and SK-Hep1, respectively. Treatment of cell lines with essential oil reduced the NFKB1 and TGFB1 and increased the CASP3 and TNF [62]. NF- κ B plays essential role in development, cell growth, proliferation of cells in pathological conditions such as metastases [63]. The increase in CASP3 and TNF- α imply on inducing the pro-apoptotic process through different pathways, and controlling the carcinogenesis [64].

The efficacy of asafotida (50, 100, 200 mg/kg) was evaluated in 1,2-dimethylhydrazine (DMH) induced colon cancer in Sprague Dawley rats. The animals were divided in 6 groups of 1-vehicle group (subcutaneous 1 mM Ethylene diamine tetraacetic acid

(EDTA) saline, every week), 2–30 mg/kg DMH dissolved in 1 mM EDTA every week, 3–5, oral pretreatment of animals with 50, 100, 200 g/kg body weight and weakly DMH injections, 6- pretreatment of animals with 200 mg/kg asafotida aqueous extract. The animals were treated for 16 weeks. The body weight, colon tumor, and total sialic acid were determined in different groups. The gross morphology of histopathology samples was determined under light microscope. After 16 weeks of treatment, the body weight changes were determined, and the results exhibited that DMH administration for 16 weeks significantly reduced the body weight from 279.16 ± 16.25 to 221.5 ± 14.74 g. Co-administration of asafotida aqueous extract in DMH treated animals increased the body weight in comparison with DMH group and improved the overall body metabolism. The tumor incidence was 100% in DMH group, while the incidence of tumor reduced to 66.6%, 50%, and 50% in 50, 100, 200 mg/kg asafotida treated animals. The incidence of tumor (%) was zero at control and asafotida group. The mean of tumor multiplicity per animals was 2.5 in DMH group, followed by 50 (1.33), 100 (1.0), and 200 (1.17) mg/kg asafotida, respectively. The tumor size (cm) was 0.88 ± 0.01 in DMH group and reduced to 0.75 ± 0.04 and 0.66 ± 0.12 cm in 5 and 100 mg asafotida groups. 200 mg/kg asafotida reduced the tumor size in DMH treated group to 0.71 ± 0.07 cm. DMH significantly increased the thiol-specific antioxidant (TSA) levels in serum of rats from 29.66 ± 2.29 mg/dl in control group to 53.41 ± 3.46 mg/dl in DMH group. The TSA levels were 44.38 ± 1.29 , 39.44 ± 4.74 , and 41.16 ± 3.96 mg/dl in different concentrations of asafotida groups. The amount of TSA was 32.19 ± 2.49 in 200 mg/kg asafotida group alone. Histopathology samples of different groups exhibited the normal colonic structure, while in DMH; the abnormal colon had irregular glands. An improvement in irregular mucosal lining in architecture of colon was observed in asafotida treated animals. The lower focal inflammations were observed in asafotida treated animals. The improvement in colon architecture was better in higher concentration of asafotida (100 mg/kg), in comparison with 50, and 200 mg/kg asafotida aqueous extract [65]. The chemo protective effects of asafotida were confirmed against colon cancer in DMH treated animals. The tumor incidence, tumor size, and colon architecture and the total sialic acid level improved in presence of asafotida gum. During the carcinogenesis, the total sialic acid increased in serum as the result of cellular proliferation. The mechanism responsible for chemo-preventive effects of asafotida may be

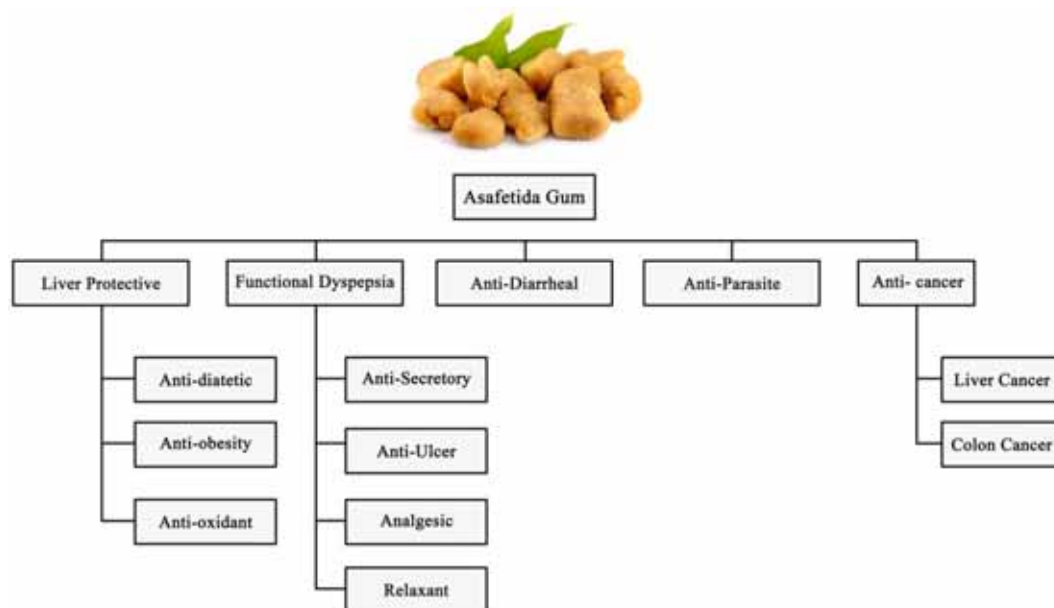


Fig. 2. The efficacy of asafetida gum in treatment of gastrointestinal disorders.

related to the presence of antioxidant components such as ferulic acid with anticancer effects against breast and colon cancer [66]. Galbanic acid induced the apoptosis in cancerous cell lines by activation of caspase and inhibition of Mcl-1 [67]. Vinyl disulfides from asafetida activated the TRPA1 [68]. Oral administration of asafetida increased the life span in mice animal model [69]. Different mechanisms provide a mechanistic basis for potential beneficial health claims associated to the use of asafetida.

2.9. Safety and dose of *F. asafetida*

The LD₅₀ of asafetida aqueous extract was 1600 mg/kg in mice [3]. Evaluation of asafetida (12.5, 25, 50 and 100 mg/kg) for 30 days on hepatic (AST, ALT, ALP), renal (Urea, Cr), cardiac (CPK) and blood biochemical parameters (Pt, Ptt) of male Wistar rats showed pre-treatment of animals with asafetida significantly reduced the plasma level of AST, CPK and Ptt ($P < 0.05$). High doses of asafetida reduced the plasma urea concentration and increased the plasma Cr concentration and blood pressures. The low dose of asafetida (25 mg/kg) is a safe dose without any side effects [70]. The results of acute toxicity test of asafetida water suspension exhibited that 100 mg/kg asafetida was safe without toxicity effects [33].

Asafetida is abortifacient, its use is not recommended during pregnancy and lactation. The fatal hemoglobin is oxidized by asafetida, while asafetida had no effect on adult hemoglobin [1]. The oral use of asafetida gum resin in infants lower

than 4 months are associated with risk of methemoglobinemia due to deficiency in glucose-6-phosphate dehydrogenase [71]. There is one report on reduction of blood hemoglobin in 5 months child, who received undefined dose of asafetida resin [72]. The allergic and skin sensitivity is reported in people with allergic to Umbelliferae family. The activity of warfarin is enhanced by asafetida [73] and asafetida has deleterious effects on sister chromatids of sperm and spermatocytes [74].

Different concentrations of asafetida (10, 50, 100, 250, 2000, 5000 $\mu\text{g/g}$) orally for 32 days (four cycles of spermatogenesis) was administrated in non-inbred male Swiss A mice. No aberrations were observed at concentration of 50 μg , but the break and translocations increased in a dose dependent manner and the minimum dose of asafetida to mouse translocate is 0.8 g. Low concentration of 7-hydroxycoumarin in asafetida can be mutagenic for mammalian chromosomes. Although, 15 g asafetida had no mutagenic effect on cultured human leucocytes, asafetida treated male mice with female mice for 15 days had not given rise to a pregnancy. Totally, asafetida caused structural chromosomal aberrations in primary spermatocytes of mice and with increase in asafetida concentrations; the frequency of chromosomal aberrations was not linear, and a few abnormalities were seen in spontaneous polyploid cells [75]. Oral administration of asafetida (0.5 and 1 g/kg body weight) induced a weak sister chromatid exchange in spermatogonia [74]. Wheat flour, other cheap oleo-gum resin, and small stone

particles are adulterations in asafoetida gum [76]. Oral asafoetida extract (5 g/kg) had no toxic effect in rats [56].

0.3–1 g asafoetida resin 3 × /day or 2–4 ml asafoetida tincture, or 20 drops of tincture are recommended doses. The dose of resin is not determined correctly, but in India, 200–300 mg asafoetida resin is used for treatment of kidney and gall stones [77].

3. Conclusion

Asafoetida gum is used in different traditional systems for treatment of gastrointestinal diseases. Asafoetida gum is used for treatment of dyspepsia, worm, cancers, and many other diseases according to its traditional belief. In modern medicine, the efficacy of asafoetida gum aqueous extract was the subject of experimental studies. The garlic odor of asafoetida is secreted from breath, and gastric secretions. According to Chinese believes, asafoetida resin can enter into the liver, spleen and the channels of stomach and stimulate them [23].

The liver protective effects of asafoetida against the toxic effects of arsenic and CCL₄ were confirmed in animal studies. There is one clinical study on efficacy of asafoetida gum aqueous extract in functional dyspepsia, and it seems that the analgesic, anti-inflammatory, anti-ulcer and anti-secretory effects of asafoetida gum play an important role in its efficacy in functional dyspepsia. The anti-diarrheal, anti-parasite and anti-cancer effects of asafoetida have been limited to experimental studies (Fig. 2) and required more investigations. Although, asafoetida is safe in lower doses, but take care about the correct dose should be considered in human and animal studies. The stinky odor of asafetida is other subject that should be considered in formulations.

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Conflict of interest

The authors declare that there is no competing of interest.

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Authors' contributions

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