

ALOE FEROX: A PROMISING THERAPY FOR IRRITABLE BOWEL SYNDROME

Introduction

Constipation is the most common digestive complaint in the United States, outnumbering all other chronic digestive conditions. Moreover, constipation is associated with irritable bowel syndrome (IBS) in 59% of cases, and IBS affects approximately 36 to 54 million Americans.^{1,2}

The following overview of constipation and IBS-related constipation will address the costs associated with IBS, its pathogenesis, and the current medication options for its treatment. This overview will also address the efficacy and safety of aloe ferox, an herb indigenous to South Africa, for the treatment of constipation and IBS-related constipation.

The Costs of Constipation and IBS-Related Constipation

Constipation-related healthcare costs total \$6.9 billion in the US annually, and Talley et al. estimated that the healthcare costs accrued in the US for the treatment of IBS are over \$8 billion per year.^{3,4,5} Levy et al. found that the total costs of care for IBS patients were 49% higher than for population controls during the index year (starting with the visit at which IBS patients were diagnosed).⁶ In the US, IBS accounts for 3.5 million physician visits annually, and it is the most common cause of referrals to gastroenterologists.^{7,8}

The Pathogenesis of IBS

The ambiguities involved in defining IBS, lack of understanding of its pathophysiology, and slow accumulation of evidence on the benefits of treatment modalities have made IBS notoriously difficult to diagnose and treat.⁹ Numerous mechanisms have been purported to explain the cause of IBS, and scientists currently believe that IBS represents a multitude of aberrations that include dysmotility, visceral hypersensitivity, abnormal brain-gut responses, psychosocial factors, sensorimotor dysfunction, and alterations in local reflex mechanisms or extrinsic and central neural connections.¹⁰ Various bacteria and viruses have also been associated with the pathogenesis of IBS.^{11,12}

The understanding of IBS is exacerbated by the complexity of the enteric nervous system, which is composed of a vast network of neurons located throughout the GI tract.¹³ This neuronal network communicates directly with the brain through the spinal cord. There are as many neurons in the small intestine as in the spinal cord, and the same hormones and chemicals that transmit signals in the brain have been found in the gut, including serotonin, norepinephrine, nitric oxide, and acetylcholine.¹³

The Conundrum of Treating IBS

Current interventions for IBS with constipation tend to target single symptoms of the disorder, with multiple symptom relief only achieved through the use of multiple therapies.¹⁴ Hence, there remains an unmet need for well-tolerated and effective treatments for IBS with constipation that target abdominal symptoms,

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including abdominal pain and bowel symptoms.¹⁵

Conventional therapy for patients with moderate to severe symptoms of IBS is largely unsatisfactory, and the development of new and effective drugs is made difficult by the disease's complex pathogenesis, variety of symptoms, and lack of objective clinical findings that are the hallmark of this disorder.¹⁵

Current Medications for the Treatment of IBS

The various medications that are used to treat IBS include laxatives, antispasmodics, lubiprostone, and recently FDA-approved linaclotide. Given the staggering scope and costs of IBS-related constipation pharmaceutical companies have poured millions of dollars into research and development for IBS, but their massive investments have yielded largely ineffective medications and, in some cases, medications that are deleterious.

For example, Novartis' tegaserod, a serotonin agonist, was hailed as a potential panacea for the treatment of IBS. The FDA approved the drug in 2002, but it was subsequently removed from the market in 2007 due to FDA concerns about its adverse cardiovascular effects.

Lubiprostone (Sucampo/Takeda/Abbott), a chloride channel activator, is FDA approved for adult women and men who have IBS with constipation. A phase III study found that patients treated with lubiprostone experienced a median increase of three or four spontaneous bowel movements per week after one month of treatment with lubiprostone compared with a median increase of 1.0 to 1.5 spontaneous bowel movements per week among those in the placebo

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group.¹⁶ In clinical trials, the most common adverse event for lubiprostone has been nausea (31%). The drug's adverse events also included diarrhea (13%), headache (13%), abdominal distention (5%), abdominal pain (5%), flatulence (6%), sinusitis (5%) and vomiting (5%).¹⁷ Lubiprostone affects on pregnancy have not been studied in humans, but testing in Guinea pigs resulted in fetal loss. The side effect profile of lubiprostone has generated disappointing sales in the US—\$240 million in 2012.

Linaclotide (Ironwood/Forest Laboratories), a peptide agonist of guanylate cyclase 2C, was approved by the FDA for the treatment of irritable bowel syndrome with constipation and chronic idiopathic constipation in 2012. A phase III study of people with chronic constipation showed that one in five patients returned to normal bowel movements after taking linaclotide.¹⁸ And on average, chronic constipation patients taking linaclotide had more frequent bowel movements, less straining, and less bloating and discomfort.¹⁹ Although linaclotide seems to lack the efficacy of lubiprostone, its side effect profile is far superior to lubiprostone. Cantor Fitzgerald & Co. expects linaclotide to overtake lubiprostone sales by 2015 and reach sales of \$2.8 billion by 2027.

A number of probiotics are currently in phase II and phase III trials for the treatment of IBS. Recent studies have suggested that probiotics may be useful in the treatment of IBS.²⁰ Although the exact mechanism for how probiotics may aid in the reduction of IBS symptoms is unknown, the effects of probiotics on alterations in gut bacteria appear to play a role in probiotics mitigation of IBS symptoms.²⁰

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Despite an increasing understanding IBS, over-the-counter (OTC) laxatives remain the primary treatment option for severe constipation and IBS-related constipation, and the annual expenditures on OTC laxatives in the US is estimated to exceed \$850 million.²¹

Although OTC laxatives are the principal treatment for IBS-related constipation in the US, they are an extremely imperfect treatment. Laxatives are habit forming and addictive, because they ultimately contribute to constipation by reducing the bowel's normal activity.²² As a consequence, increasingly large doses of laxatives are required to achieve regular bowel movements, and they ultimately become utterly ineffectual.²² Laxative abuse can also lead to potentially fatal fluid and electrolyte imbalances—including hypokalaemia and metabolic acidosis—as well as intestinal paralysis, IBS, pancreatitis, and renal failure.

^{23,24,25}

Aloe Ferox for the Treatment of IBS

Aloe ferox is in the *Aloe* family of flowering plants, and its most frequently cited medicinal uses include the treatment of infections, internal parasites, digestive ailments, and injuries.²⁶ Indeed, studies have shown that aloe ferox is effective against bacteria, fungi, and a variety of different parasites.^{27, 28} Moreover, studies have demonstrated that aloe ferox has strong anti-oxidant activities and anti-inflammatory properties too.^{29,30}

Although aloe ferox has been used to treat digestive tract ailments in South Africa for generations, only two studies in PubMed, a vast repository of scientific studies, address its efficacy and safety in the treatment of constipation.

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In the first study, Wintola et al. assessed the efficacy of aloe ferox extract against loperamide-induced constipation in Wistar rats at the respective dose ranges of 50, 100, and 200 mg/kg body weight per day. The study found that aloe ferox improved intestinal motility, increased fecal volume, and normalized body weight in the constipated rats, which are indications of the herb's laxative properties of the herb, and Wintola et al. determined that the 200 mg/kg body weight dose of aloe ferox extract showed optimum motility efficacy.³¹ The researchers concluded that the effect of aloe ferox extract compares favorably well with senokot, a standard laxative drug.³¹

A second study evaluated the safety of aloe ferox for the treatment of constipation in Wistar rats. This study evaluated the toxicological effect of aloe ferox on hematological parameters as well as liver and kidney function indices in loperamide-induced constipated rats. Aloe ferox did not cause any significant effect on liver and kidney function indices, including serum levels of creatinine, uric acid, urea, calcium and potassium ions at all the dosages investigated, whereas OTC laxatives have demonstrated a negative effect on electrolyte imbalances.³² The serum levels of total protein, albumin, bilirubin and gamma glutamyl transferase were not affected by aloe ferox, and, conversely, the elevated activities of alkaline phosphatase, alanine transaminase and aspartate transaminase in the untreated constipated animals were normalized following treatment with aloe ferox. The researchers findings indicated that aloe ferox may be a safe oral remedy for constipation.³²

Despite a dearth of studies concerning the efficacy and safety of aloe

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ferox for the treatment of constipation and IBS-related constipation, a number of anecdotal accounts have buttressed the efficacy and safety of aloe ferox for the treatment of IBS. As previously mentioned, IBS is thought to be an amalgam of different disorders, and anecdotal accounts of people who take aloe ferox for IBS suggest that aloe ferox has more of a universal mitigation of symptoms than the current medications that are used to treat IBS.

An explanation for aloe ferox mitigating a number of symptoms for IBS is that the herb has properties that are effective against bacteria, fungi, and a variety of different parasites, and it has also demonstrated strong anti-oxidant activities and anti-inflammatory properties too. So aloe ferox appears to affect various disorders that play a role in IBS. Moreover, aloe ferox differs from OTC laxatives, because it is not habit forming and addictive. Anecdotal accounts indicate that increasingly large doses of aloe ferox are not required for regular, daily bowel movements.

The Safety and Anti-Carcinogenic Effects of the Aloes

Although aloe ferox has been used as a medicinal herb for centuries, its overall sales as an herbal supplement are overshadowed by aloe vera, which is also indigenous to Africa. Symphony IRI Group, a Chicago-based market research firm, ranks aloe vera as the 18th top-selling herbal supplement in the US with 2012 sales of \$2.52 million, whereas sales of aloe ferox did not pierce the top 40 of herbal supplement sales in the US. Aloe vera gel can be found in hundreds of skin products, including lotions and sunblocks. The Food and Drug

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Administration (FDA) has also approved aloe vera as a natural food flavoring, and its available in soft drinks that are sold in numerous retail stores, including WalMart.

Fanali et al. conducted a chromatographic analysis of both aloe ferox and aloe vera, and their analysis found that both plants share a number of chromatographic chemical properties.³³ But a primary difference in the chromatographic properties between the two plants was the presence of the anthraquinones aloin A and aloin B.³³ Although both aloe ferox and aloe vera contain aloin A and aloin B, aloe ferox has twofold to fivefold greater concentrations of aloin A and aloin B.³³ The aloins play an integral role in the plants' laxative properties.^{34,35,36,37,38,39,40}

In addition to having a laxative effect, Hamiza et al. found that aloin "clearly" protects against chemically-induced preneoplastic lesions in Wister rats by inducing antioxidant, anti-inflammatory and antiproliferative markers.⁴¹ Moreover, several studies have demonstrated that aloin has potent anti-tumor and cancer properties.^{42,43,44,45,45,47,48,49,50,51}

The aloe species also contains aloctin, which is a glycoprotein with immunomodulatory effects against cancer.⁵³ For example, Ehrlich ascites are manifestations of advanced cancers of abdominal cavity organs such as colon cancer, and Akev et al. have shown that aloin significantly reduced Ehrlich ascites tumors in mice.⁵⁴ Aloin has significantly inhibited the development of Shay ulcers and indomethacin-induced gastric lesions in rats too.⁵⁵ Additional researchers have also found that aloin has potent anti-tumor activities.^{55,57,58}

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Both aloe vera and aloe ferox contain aloe-emodin, which has also demonstrated potent anti-tumor activities.⁵⁹ Two studies by Subjoj et al., published in the *Journal of Pharmacology* and *European Journal of Pharmacological Science*, respectively, found that aloe-emodin acted on multiple cellular mechanisms to arrest and inhibit colon cancer.^{60,61}

Although aloe ferox and aloe vera share chromatographic properties, aloe ferox contains a twofold to fivefold greater concentration of aloin A and aloin B.³³ The previously discussed data demonstrates that the aloins play an integral role in the laxative properties of both aloe ferox and aloe vera.^{34,35,36,37,38,39,40} The aforementioned data also demonstrates that the aloins have potent anti-tumor and anti-cancer properties.^{41,42,43,44,45,45,47,48,49,50,51}

As mentioned, aloin is an anthraquinone, a class of naturally occurring phenolic compounds, and the anthraquinones are frequently found in laxatives. For example, the anthraquinone senna is the active ingredient of Ex-Lax and several other laxatives. Several studies have demonstrated the anti-tumor effects of both aloin and senna. However, aloin has been shown to decrease carcinogenic activity in the colon that has been induced in rodents by azoxymethane, but senna has been shown to promote carcinogenic activity in the colon that has been induced in rodents by azoxymethane.^{88,89}

Conclusion

Aloe ferox is an herb that has relieved the symptoms of thousands and

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thousands of people who are afflicted with IBS. As a laxative, aloe ferox differs from senna, because it is not habit forming in the respect that it does not require increasingly large doses to achieve regular bowel movements, whereas senna is habit forming and addictive due to the fact that it ultimately contributes to constipation by reducing the bowel's normal activity.²²

At present, it is not known if the relatively large amounts of aloin contained in aloe ferox are solely responsible for its unique laxative properties or if other compounds contained in the herb contribute to its unique laxative properties too. So further research will be required to determine if the unique laxative properties of aloe ferox are solely a function of aloin or if other compounds contained in the herb contribute to its unique laxative profile.

Aloe ferox contains a twofold to fivefold greater concentration of aloin, which not only imparts laxative properties to the herb, but aloin is also a potent inhibitor of carcinogenesis. Thus, aloe ferox and aloe vera are fundamentally different herbs when looked at from the prospective of inducing motility in the intestinal tract.

The FDA-approved lubiprostone (Amitiza™), marketed by Sucampo, Takeda, and Abbott, which is approved for the treatment of IBS with constipation, however it shows to only produced a mere median increase of three or four spontaneous bowel movements per week, and its associated with a plethora of side effects.^{16,17} Lubiprostone has also been shown to be teratogenic in guinea pigs, but aloin A administered to pregnant rats at 200 mg/kg per day between the 10th and 13th day of their gestational period was found to have no teratogenic or

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foetotoxic effects.⁹⁰

Linaclotide (Linzess™), the latest FDA-approved medication for the treatment of IBS with constipation, even though only one in five patients experience marginal benefit in bowel function improvement.¹⁸

Further research is invariably required on aloe ferox and aloin. But according to numerous anecdotal accounts, aloe ferox restores IBS patients to daily or near daily bowel movements without the concomitant side effects of lubiprostone, linaclotide and OTC laxatives, so it has the potential to dominate the IBS market.

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