

# The Potential Application of *Aloe Barbadensis* Mill. as Chinese Medicine for Constipation: Mini-Review

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**Abstract:** *Aloe barbadensis* Mill. has a long history of medicinal use in the annals of traditional Chinese medicine, wherein it has garnered considerable renown. Its multifaceted therapeutic properties, characterized by its anti-inflammatory and antibacterial attributes, alongside its established efficacy as a laxative agent, have been extensively documented. This review commences with an exploration of the nomenclature, fundamental characteristics, and principal constituents of *Aloe barbadensis* Mill. responsible for its laxative effects. Subsequently, we delve into an extensive examination of the molecular mechanisms underlying *Aloe barbadensis* Mill.'s laxative properties, types of constipation treatments, commercially available preparations, considerations pertaining to toxicity, and its clinical applications. This review aims to serve as a comprehensive reference point for healthcare professionals and researchers, fostering an enhanced understanding of the optimal utilization of *Aloe barbadensis* Mill. in the treatment of constipation.

**Keywords:** *Aloe barbadensis* Mill, constipation, laxative

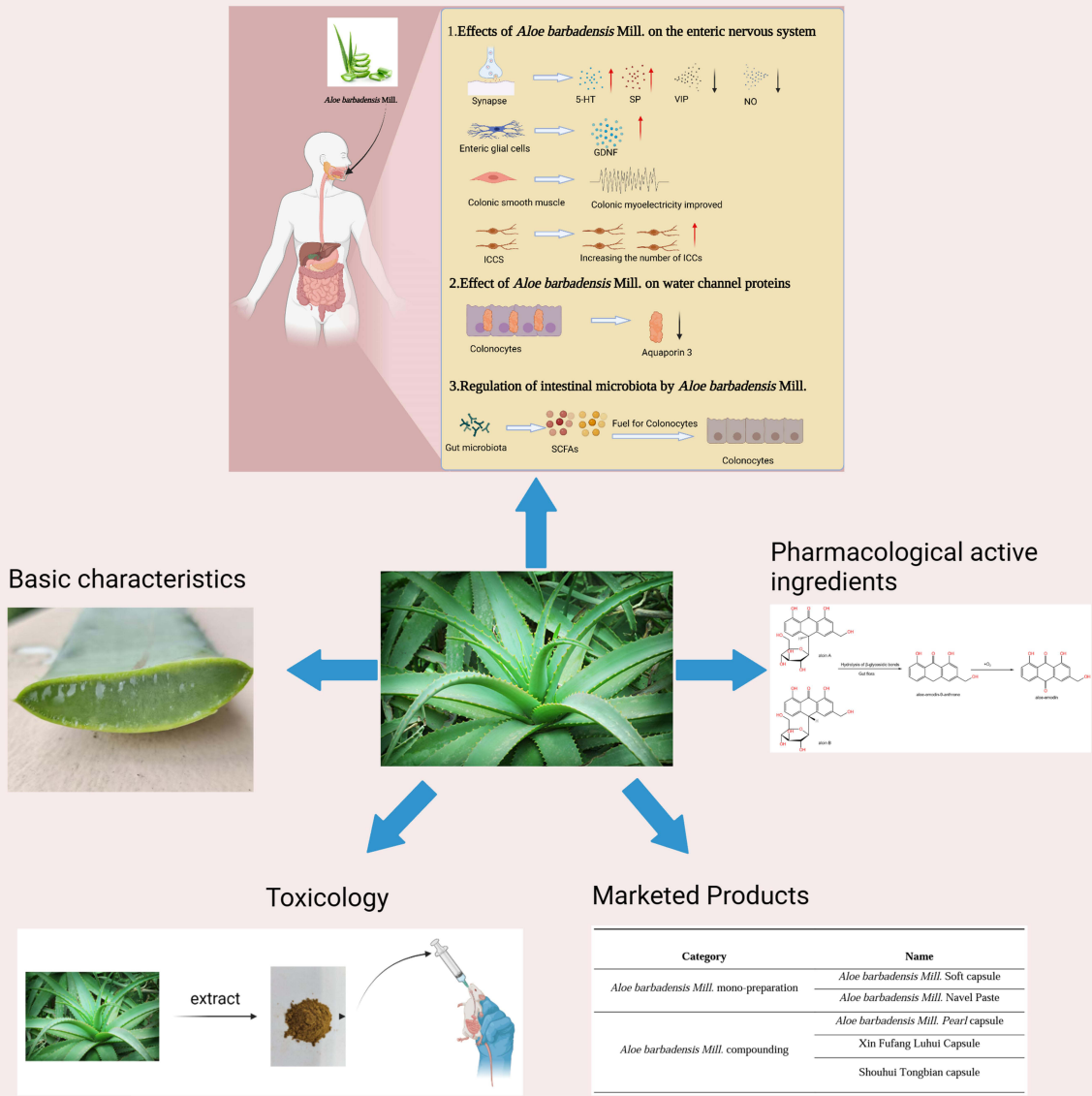
## Introduction

Constipation is a prevalent gastrointestinal disorder with a global incidence ranging between 12% and 19%.<sup>1</sup> Owing to the impact of occupational circumstances, a substantial proportion of individuals, roughly 70%, in contemporary society are in a suboptimal state of health, characterized by gastrointestinal discomfort, of which constipation is a predominant manifestation.<sup>2</sup> The pathophysiology of this disorder is intricate, often arising from a confluence of factors. Although constipation lacks a standardized definition, it is generally typified by clinical indicators encompassing infrequent bowel movements (typically occurring less than three times per week), diminished fecal water content, heightened straining during defecation, and a pervasive sense of incomplete bowel evacuation.<sup>3</sup> Prolonged instances of constipation may instigate complications such as rectal prolapse, pubic nerve damage, and hemorrhoids. Furthermore, constipation commonly recurs, and its chronic nature can detrimentally affect the patient's quality of life, inducing psychological distress and perpetuating a cyclical exacerbation of constipation symptoms.

*Aloe barbadensis* Mill. is an enduring succulent known for its tenacity in arid environments.<sup>4</sup> It has garnered substantial scientific attention due to its historical utilization in traditional medicine.<sup>5</sup> *Aloe barbadensis* Mill. exhibits a multitude of pharmacological activities, such as treatment for constipation, anti-inflammatory, anti-obesity, and blood glucose and cholesterol regulatory effects.<sup>6</sup> The origin of its name can be traced back to the Arabic term “alloe” and the Hebrew term “allal”, both denoting the extraction of bitter sap from the plant's leaves. *Aloe barbadensis* Mill., a versatile plant, exhibits a multitude of names, reflecting the diverse geographical and cultural contexts in which it is cultivated. In

Graphical Abstract

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Mechanisms for treating constipation



Latin, French, Portuguese, and German, it is referred to as “Aloe”, while in English, it is commonly known as “Crocodile’s Tongue”. Other regional names include “Jadam” in Malaysia, “Luhui” in China, “*Sa’villa*” in Spain, “*Musabbar*” in India, “*Ailwa*” among Indians, “*Sabbar*” in Arabic, and “*Nassau*” in the Philippines.<sup>7</sup> This array of nomenclature exemplifies the rich linguistic and cultural heritage associated with *Aloe barbadensis* Mill.

*Aloe barbadensis* Mill. has accrued a rich historical legacy as an agent of therapeutic significance, both topically and orally, in the management of constipation across diverse regions worldwide. This review covers the literature between March 1958 and September 2023. With the keywords *Aloe barbadensis* Mill., aloin, aloin-emodin, laxative, and

constipation, the literature is retrieved from electronic databases, such as Web of Science, Elsevier Science Direct, PubMed, CNKI, and others.

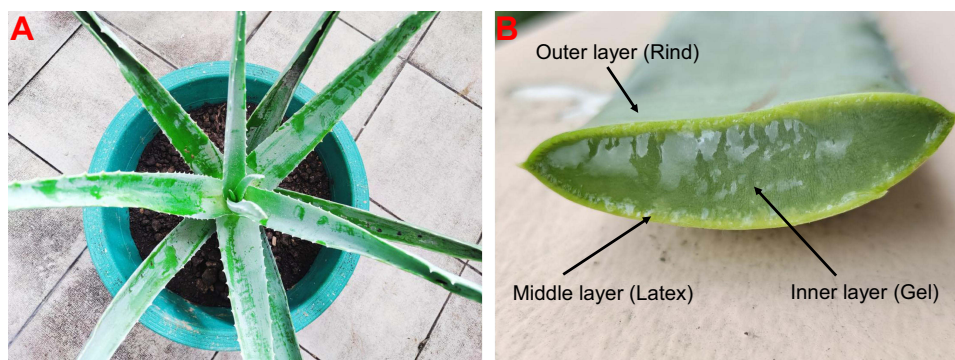
## The Basic Characteristics of *Aloe barbadensis* Mill

### Structural Composition of *Aloe barbadensis* Mill

*Aloe barbadensis* Mill., originating from the Arabian Peninsula, was introduced to the island of Curacao in the 16th century by Spanish colonizers.<sup>8</sup> Among the 300 dispersed aloe species worldwide, certain species such as *Aloe ferox* Mill., *Aloe arborescens* Mill., and *Aloe barbadensis* Mill. are recognized as being edible. However, *Aloe barbadensis* Mill. are distinguished for their medicinal properties and demonstrating the most potent therapeutic value. As a consequence, *Aloe barbadensis* Mill. has been the subject of extensive research, emerging as the most extensively investigated and promising species of *Aloe barbadensis* Mill., with a diverse range of applications in the development of food, health products, and cosmetics.<sup>9</sup> The leaves of *Aloe barbadensis* Mill. are long and plump, varying in width, generally triangular or elliptical, with numerous small bumps on the leaf surface, and are covered with a white powder (Figure 1A). Aloe curacao can be divided into three parts, the outer, middle, and inner layer (Figure 1B). The outer layer, commonly known as the epidermis layer, comprises a robust and rigid cuticularized skin that endows the plant with protective attributes and serves as a site for synthesizing essential biomolecules including carbohydrates and proteins.<sup>10</sup> The inner layer (gel layer) is the transparent gel where *Aloe barbadensis* Mill. stores nutrients and is rich in polysaccharides, minerals, proteins, vitamins (A, B, C, and E), and other active ingredients.<sup>11</sup> The middle layer (latex layer) contains yellow latex-like mucilage that acts as a barrier to preserve the inner gel in a sterile state.<sup>12</sup>

### Processing of *Aloe barbadensis* Mill

*Aloe barbadensis* Mill., a well-established botanical entity acclaimed for its medicinal attributes, presents itself in four discernible extracted manifestations: gel, dry powder, latex, and whole leaf extract.<sup>13</sup> *Aloe barbadensis* Mill. undergoes various processing methods to derive different products. The first method involves fresh leaf processing, whereby the harvested *Aloe barbadensis* Mill. leaves are meticulously cleaned, cut, peeled, and de-thorned to yield *Aloe barbadensis* Mill. gel or fresh juice.<sup>14</sup> Alternatively, the second method, dry leaf processing, entails air-drying or arching the harvested leaves, resulting in the production of dry leaves or dry powder.<sup>15</sup> The third technique, known as emulsion processing, involves cutting the *Aloe barbadensis* Mill. leaves to collect the bitter yellow liquid that flows out. Subsequently, this liquid is boiled to obtain a thick paste-like substance, which is then sun-dried, resulting in the formation of a black solid, recognized as the traditional Chinese medicine *Aloe barbadensis* Mill.<sup>16</sup> Finally, in the whole leaf extract processing method, the *Aloe barbadensis* Mill. leaves are meticulously cleaned, cut, peeled, and de-stemmed, then these processed leaves are then subjected to solvent extraction, yielding the whole leaf extract.<sup>17</sup>



**Figure 1** (A) *Aloe barbadensis* Mill. and (B) its Structure.

# The Historical and Traditional Use of *Aloe barbadensis* Mill. for Constipation

## Traditional Use as a Natural Remedy for Constipation

The therapeutic potential of *Aloe barbadensis* Mill. has been meticulously documented throughout history (Figure 2), with its earliest known utilization dating back to 1550 BC as evidenced in the “Ebers Papyrus”, an ancient Egyptian medical manuscript.<sup>18</sup> This ancient text notably underscores the medicinal applications of *Aloe barbadensis* Mill. during that era. Moreover, a captivating legend surrounds *Aloe barbadensis* Mill., with the plant holding immense significance for the Pharaohs of ancient Egypt due to its perceived capacity to bestow longevity. Funeral customs mandated the inclusion of an aloe staff as a symbol of rebirth, presented to the deceased during the ceremony. *Aloe barbadensis* Mill. was also extensively cultivated in proximity to the pyramids and along the routes leading to the Valley of the Kings. It was believed to offer sustenance and care to the Pharaoh on their journey to the afterlife. The blossoming of *Aloe barbadensis* Mill. was considered a favorable omen, signifying the successful transition of the departed soul to the ‘other shore’.<sup>19</sup> Over a millennium and a half later, the Greek physician Dioscorides provided the earliest comprehensive description of the pharmacological effects of *Aloe barbadensis* Mill. in his “De Materia Medica” written in 50 BC.<sup>20</sup> Dioscorides emphasized that the juice of *Aloe barbadensis* Mill., rather than the gel, was the active component for treating constipation. Processed *Aloe barbadensis* Mill., as dried *Aloe barbadensis* Mill. juice, was introduced to England in 1300 AD to alleviate gastrointestinal disorders. Eventually, *Aloe barbadensis* Mill. was recognized as a remedy for constipation in the United States Pharmacopoeia in 1820.<sup>21</sup> In the Oriental region, during the late Sui and early Tang dynasties, traders of Arab origin introduced *Aloe barbadensis* Mill. to China. The first written record of *Aloe barbadensis* Mill. in China is found in the “Treatise on Medicinal Properties”, written by Zhen Quan during the Tang dynasty, in which he reported *Aloe barbadensis* Mill.’s efficacy in treating “children’s chancre”. During the Song Dynasty, the “Kai Bao Ben Cao”, compiled by Liu Han, documented *Aloe barbadensis* Mill.’s effectiveness in treating “three insects”, hemorrhoidal fistulas, and croton poisoning. Li Shizhen’s “Compendium of Materia Medica”, written during the Ming Dynasty, specified that *Aloe barbadensis* Mill. was used to treat children’s spleen chancre.<sup>22</sup> “The contemporary National Pharmacopoeia Committee documented the medicinal properties of *Aloe barbadensis* Mill. in the Chinese



**Figure 2** Historical Texts Documenting the Efficacy of *Aloe barbadensis* Mill. in Treating Constipation.



Pharmacopoeia, describing it as diaphoretic and treatment for constipation, able to clear liver and fire, kill worms and treat noma". Above all, we reviewed the utilization of *Aloe barbadensis* Mill. for ameliorating constipation has been widely documented across Western and Eastern medicinal practices. This historical deployment underscores the enduring acknowledgment of the potential therapeutic advantages associated with *Aloe barbadensis* Mill.

## Pharmacological Activity of Aloe Barbadensis Mill

The therapeutic efficacy of *Aloe barbadensis* Mill. stems from its abundant repertoire of bioactive constituents, primarily sourced from the gel and latex, two anatomically distinct segments of the plant. These specialized constituents encompass a multitude of active compounds, which collectively contribute to the extensive array of biological functionalities displayed by *Aloe barbadensis* Mill. This part delves into the intricate interplay of these bioactive constituents, shedding light on their individual and synergistic contributions to the plant's therapeutic properties.

## Pharmacological Active Sites of Aloe Barbadensis Mill

### Aloe Barbadensis Mill. Gel

The gel residing within the leaves of *Aloe barbadensis* Mill. encompasses a diverse array of polysaccharides, vitamins, minerals, enzymes, and amino acids, thereby manifesting an extensive range of pharmacological properties including antidiabetic, immunomodulatory, anti-inflammatory, antioxidant, wound-healing promotion, anticancer, hepatoprotective, and antibacterial activities, among others.<sup>23</sup> The NMR spectrum of *Aloe barbadensis* Mill. by Bozzi et al<sup>24</sup> clearly exhibits signals corresponding to glucose, malic acid, and the polysaccharide acemannan, which are the three primary natural components found in *Aloe barbadensis* Mill. gel. A recent investigation has demonstrated the potential of *Aloe barbadensis* Mill. gel in mitigating the deleterious effects of non-steroidal anti-inflammatory drugs on the small bowel by augmenting the expression of mucin.<sup>25</sup> Furthermore, several scholarly inquiries have explored the protective properties of *Aloe barbadensis* Mill. gel on the intestinal tract in a simulated condition of acetic acid-induced colitis.<sup>26</sup> These studies suggest that *Aloe barbadensis* Mill. gel exerts a safeguarding influence on the intestinal tract through its anti-inflammatory mechanisms, thereby fostering the preservation of gastrointestinal integrity and facilitating treatment for constipation.

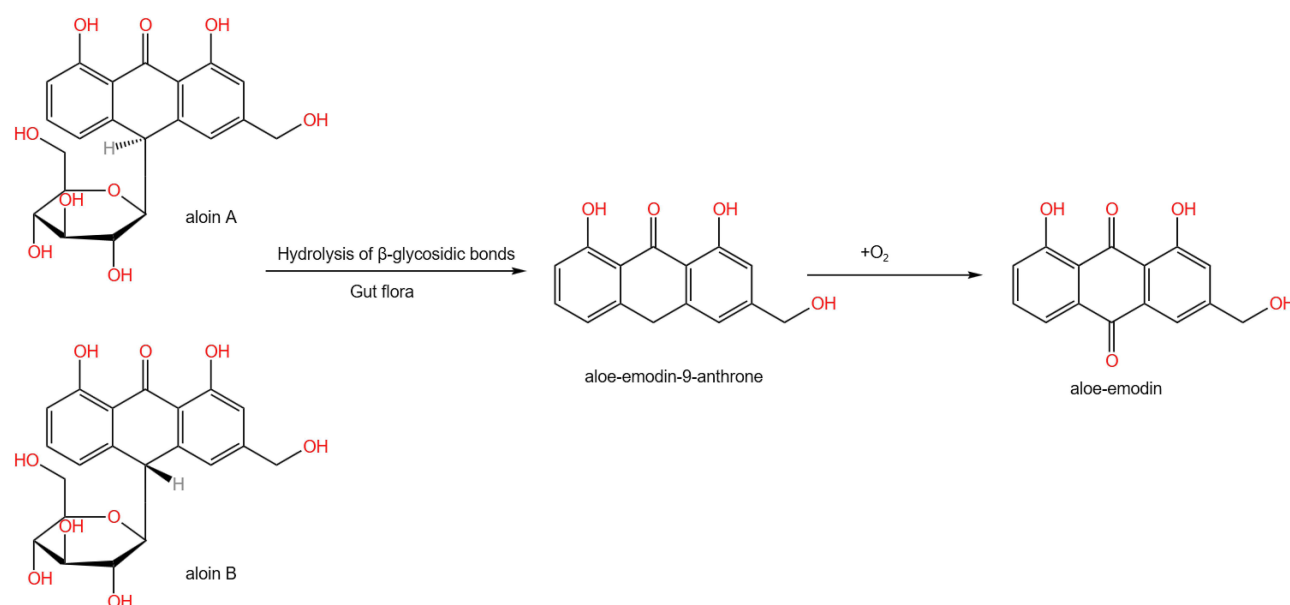
### Aloe Barbadensis Mill. Latex

In elucidating the composition of latex obtained from *Aloe barbadensis* Mill., Kim et al<sup>27</sup> employed high-performance liquid chromatography, with monitoring conducted at a wavelength of 254 nm. The principal constituents identified in *Aloe barbadensis* Mill. latex predominantly consist of anthraquinones, specifically aloin A, aloin B, aloenin A, aloenin B, and aloesin. Significantly, these components exhibit varied pharmacological properties, encompassing analgesic, anti-inflammatory, antioxidant, and constipation-treatment effects. This exhaustive analysis, utilizing high-performance liquid chromatography, serves to furnish valuable insights into the chemical composition of *Aloe barbadensis* Mill. latex,

## The Main Treatment for Constipation Pharmacological Active Ingredient —aloin

### Molecular Mechanisms of Aloin in the Treatment of Constipation

Aloin ( $C_{21}H_{22}O_9$ ) is the primary active component in this layer of latex and is usually present in *Aloe barbadensis* Mill. as a pair of non-corresponding isomers, aloin A (barbaloin), and aloin B (iso barbaloin), with aloin A being the predominant conformation. The glycosides in aloin are linked to sugars by  $\beta$ -glycosidic bonds, which are resistant to most bacterial  $\beta$ -glycosidases and can only be hydrolyzed by certain flora in the human and animal intestines. There are large differences in their hydrolysis ability by different species of intestinal flora. Generally, human intestinal flora has the strongest ability to hydrolyze the  $\beta$ -glycosidic bonds of aloin glycosides, followed by rats, and the weakest by mice.<sup>28</sup> Upon ingestion, aloin can resist degradation in the upper gastrointestinal tract and reach the large intestine, where it undergoes enzymatic hydrolysis to form glucose and aloin-9-anthrone. The latter is then reoxidized to aloin-9-anthrone<sup>29</sup> (Figure 3), which is absorbed by the intestinal epithelial cells and exerts an inhibitory effect on the  $Na^+/K^+$ -ATPase activity of the superficial epithelial cells in the distal colon.<sup>30</sup> This leads to a reduction in water and sodium reabsorption, resulting in water retention in the intestinal lumen and subsequent stool softening. Furthermore, aloin-



**Figure 3** Schematic diagram of the metabolism of aloin.

emodin can directly activate CFTR (Cystic Fibrosis Transmembrane Conductance Regulator) chloride channels, leading to the release of chloride ions into the luminal surface of epithelial cells and an increase in the concentration of chloride ions in the lumen. This results in fluid transport, which further contributes to the softening of stools and facilitates their excretion.

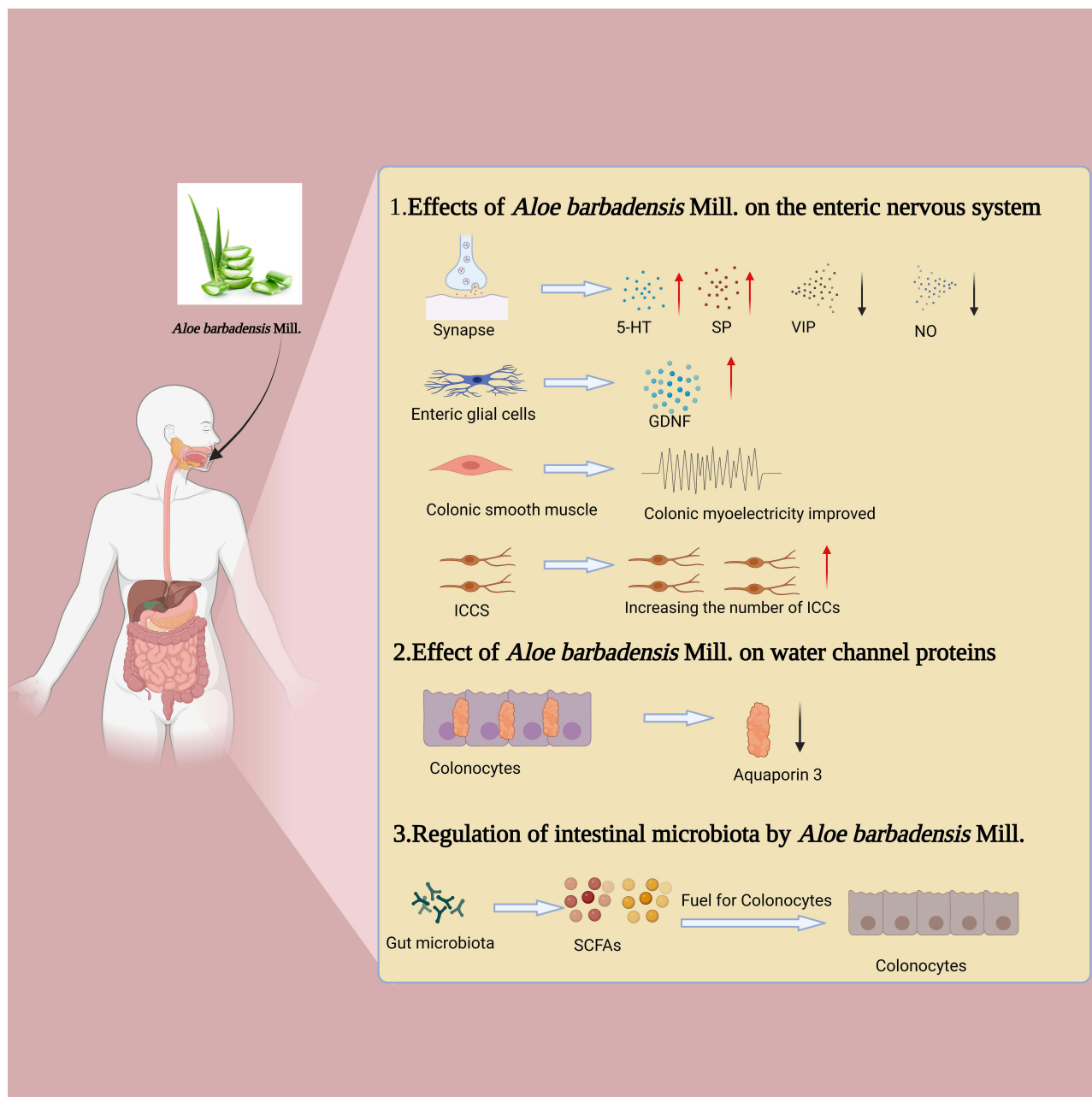
### Pharmacokinetics of Aloin

Despite being the most potent treatment for constipation compound found in *Aloe barbadensis* Mill., aloin exhibits limited oral bioavailability. In a study conducted by Niu et al, the investigation focused on assessing the absorption, bioavailability, pharmacokinetic parameters, and distribution and elimination of Aloin-A in rats following oral and intravenous administration. The study revealed that Aloin-A exhibited rapid absorption into the blood circulatory system after oral dosing, as evidenced by the attainment of a maximum plasma concentration ( $C_{max}$ ) of 412.89 ng/mL at 0.25 hours. However, the calculated absolute bioavailability of Aloin-A amounted to a mere 5.79%, thereby indicating suboptimal absorption. This phenomenon could potentially be ascribed to the expedited hydrolysis of anthraquinone glycosides catalyzed by intestinal bacteria. The pharmacokinetic analysis further demonstrated that the  $AUC_{(0-t)}$  values after oral (10 mg/kg) and iv (2 mg/kg) administration were calculated to be 391.23 and 1352.56  $\mu\text{g/L}\cdot\text{h}$ , respectively, whereas, the  $AUC_{(0-\infty)}$  values were 421.13 and 1359.86  $\mu\text{g/L}\cdot\text{h}$ , respectively. Moreover, Regarding distribution and elimination, the apparent volume of distribution of Aloin-A was significantly greater than the total blood volume in rats, indicating the extensive distribution of Aloin-A in tissues beyond the plasma. The observed half-life ( $T_{1/2}$ ) values of aloin were determined to be 3.96 hours after oral administration and 2.43 hours following intravenous administration, indicative of a swift elimination process from the blood circulatory system.<sup>31</sup> Another investigation conducted by Park et al unveiled the tissue distribution and metabolism of aloin. Tissue distribution analysis revealed the presence of aloin in diverse tissues, with the liver and intestine exhibiting the highest concentrations at 0.5 hours post-administration. Specifically, the liver demonstrated peak levels of  $77.15 \pm 15.92$  ng/g, while the intestine exhibited peak levels of  $102.37 \pm 14.12$  ng/g. However, the levels of aloin in tissues experienced a rapid decline within 90 minutes. In terms of metabolism and excretion, a considerable portion of aloin likely undergoes metabolism or excretion through feces, as evidenced by the relatively low percentage (0.03%) of the initial dose excreted in urine within 24 hours. Significantly, the urinary excretion of aloin A and aloin B collectively constituted 64.97% and 9.7% of the administered dosages, respectively, during the 24-hour period.<sup>32</sup> These findings present significant observations regarding the absorption,

distribution, metabolism, and excretion profiles of aloin within the human body, thereby establishing a significant basis for advancing the accuracy and efficacy of aloin-based interventions for constipation.

## Potential Mechanisms of *Aloe barbadensis* Mill. as Remedy for Constipation

As reported, the treatment for constipation effect of *Aloe barbadensis* Mill. was potential by influencing the enteric nervous system, water channel proteins, and gut microbiota. The multifaceted mechanisms by which *Aloe barbadensis* Mill. produces treatment for constipation effects, as illustrated in Figure 4, through which, culminates in the therapeutic aim of alleviating constipation.



**Figure 4** Potential mechanisms of *Aloe barbadensis* Mill. in the treatment of constipation. Created with Biorender.com.

## Effects of *Aloe barbadensis* Mill. On the Enteric Nervous System

The enteric nervous system (ENS) is a complex neural network composed of neurons and glial cells located within the intestinal wall, which possesses a remarkable degree of autonomy in regulating the intestinal motor, absorptive, and secretory functions, thereby earning the epithet of the “second brain” of the body.<sup>33</sup> Dysfunction of the ENS can result from various causes such as neurotransmitter imbalances, structural changes in the ganglia, and neuronal loss, leading to compromised regulatory functions and the eventual onset of constipation. Notably, *Aloe barbadensis* Mill. possesses therapeutic potential for the management of constipation by ameliorating the pathological condition of ENS.

### Neurotransmitters

An imbalance of intestinal neurotransmitters, a class of active small molecule peptides produced in endocrine and nerve cells within the gastrointestinal tract is associated with constipation. The enteric nervous system (ENS) contains two types of neurotransmitters: excitatory neurotransmitters, such as pentaxin (5-HT) and substance P (SP), which promote intestinal smooth muscle contraction and enhance intestinal propulsion; and inhibitory neurotransmitters, such as vasoactive peptide (VIP) and nitric oxide (NO), which relax intestinal smooth muscle and inhibit intestinal motility. *Aloe barbadensis* Mill. has been observed to modulate the levels of both excitatory and inhibitory neurotransmitters, thereby influencing gastrointestinal motility and intestinal fluid secretion, ultimately manifesting as a therapeutic effect in the treatment of constipation.

Tang et al conducted a study to evaluate the impact of different doses of *Aloe barbadensis* Mill. on colonic neurotransmitters in mice. The study found increased 5-HT content in mice serum, leading to an accelerated response of the intestinal wall plexus and consequently, faster intestinal peristalsis. Moreover, the intervention resulted in increased SP and decreased VIP content in mice serum, promoting the contraction of intestinal smooth muscle and enhancing intestinal propulsion.<sup>34</sup> Beck et al conducted a study that demonstrated the inhibitory effect of nitric oxide (NO) on gastrointestinal motility by reducing intracellular calcium levels and relaxing smooth muscle cells through stimulation of intracellular soluble guanylyl cyclase (sGC).<sup>35</sup> Meanwhile, Izzo et al showed that *Aloe barbadensis* Mill. can enhance smooth muscle contraction in the gastrointestinal tract and promote intestinal peristalsis by inhibiting NO synthesis.<sup>36</sup>

### Glial Cell-Derived Neurotrophic Factor

The Glial cell-derived neurotrophic factor (GDNF) is a neurotrophic factor secreted by glial cells that has demonstrated efficacy in promoting neuronal growth, differentiation, and repair. Within the digestive tract, GDNF is primarily localized to the smooth muscle cells of the gastrointestinal tract, with significantly higher expression levels observed in the colon compared to other regions. The pronounced regional distribution of GDNF within the colon suggests a crucial function in modulating the neuralization processes that govern the muscular layers of this organ.<sup>37</sup> In the context of disorders affecting the enteric nervous system, GDNF has demonstrated notable efficacy in attenuating nerve lesions and improving intestinal motility in affected colon segments.

A study has reported that individuals with constipation exhibit significantly lower serum levels of GDNF, potentially compromising the integrity of the intestinal mucosal barrier and hampering the efficiency of mucosal repair processes.<sup>38</sup> Li et al have reported that lyophilized *Aloe barbadensis* Mill. can effectively increase mRNA expression of GDNF, thus conferring therapeutic benefits in murine models of constipation by promoting repair processes within the intestinal intermuscular plexus, nourishing intestinal neurons, and modulating intestinal dynamics.<sup>39</sup>

### Electrophysiological Activity of Colonic Smooth Muscle

The electrophysiological behavior of colonic smooth muscle is primarily characterized by the presence of slow waves and fast waves of an action potential. Under normal physiological conditions, slow waves exhibit a periodic, quasi-sinusoidal electrical activity that persists regardless of whether the intestine is contracted or not, serving as a fundamental component for the initiation of action potentials in colonic smooth muscle. Therefore, modifications in the slow wave characteristics of colonic muscle electrical activity may lead to consequential changes in action potential patterns, ultimately impacting the contractile propulsive function of the colon and thereby affecting the timing of fecal expulsion.



Lu et al investigated the therapeutic effects of *Aloe barbadensis* Mill. on constipation in mice. Their study revealed an increase in the coefficient of variation for slow wave frequency and amplitude in constipated mice compared to control mice. Subsequently, following the administration of *Aloe barbadensis* Mill. treatment, a decrease in both coefficients of variation was observed in constipated mice, approaching the levels observed in the control group. These findings suggest that the intake of *Aloe barbadensis* Mill. could effectively improve abnormal smooth muscle electrophysiological activity in the colon, highlighting its potential as a therapeutic option for constipation.<sup>40</sup>

### Interstitial Cells of Cajal

The interstitial cells of Cajal (ICC) are a type of tubular cells that are widely distributed throughout the smooth muscle layer of the gastrointestinal tract. The ICCs are responsible for regulating the generation of slow waves, transducing neural electrical signals, and modulating the contraction of intestinal smooth muscle.<sup>41</sup> The expression of the C-kit gene serves as a specific marker for the identification of ICC, and the signaling pathway that is initiated by the binding of its ligand stem cell factor (SCF) regulates the proliferation and differentiation of ICC, thereby enhancing the contractile and relaxation functions of gastrointestinal smooth muscle and controlling the motility of the gastrointestinal system.<sup>42</sup>

Tong et al have demonstrated a reduction in the expression of C-kit-positive cells in the gastrointestinal tract of constipated patients.<sup>43</sup> This reduction has been shown to elicit changes in the number, volume, and ultrastructure of ICC, leading to alterations in the regularity of slow wave activity and reduced contractile movements of the gastrointestinal smooth muscle. Li's study found that after administration of aloe capsules to constipated mice, the content of C-kit in the colonic tissue of mice increased to a certain extent compared to the constipation model group, indicating that aloe could enhance the motility of intestinal smooth muscle by increasing the expression of C-kit positive cells and thus the number of ICC in the colon.<sup>44</sup>

### Effect of *Aloe barbadensis* Mill. on Aquaporins

Aquaporins (AQPs) are a class of membrane proteins that serve as water channel proteins and demonstrate broad expression throughout the gastrointestinal tract. They are involved in critical physiological processes such as cell proliferation, migration, and the modulation of intestinal inflammation, thus highlighting their significance in intestinal health.<sup>45</sup> With a molecular weight of approximately 30 kDa,<sup>46</sup> AQPs function as osmolarity-driven channels and exhibit selective transport properties for water and other minor solutes. Within the mammalian digestive system, AQPs are extensively distributed in various organs including salivary glands, esophagus, stomach, small and large intestines, liver, gallbladder, bile duct, and pancreas.<sup>47</sup> AQPs can be categorized into three groups based on their distinctive functional properties. The first group consists of classical AQPs (AQP0, AQP1, AQP2, AQP4, AQP5, AQP6, and AQP8), which exclusively exhibit selective permeability to water. The second group comprises water-glycerol channel proteins (AQP3, AQP7, AQP9, and AQP10), allowing the permeation of water, glycerol, and urea. Finally, the third group encompasses non-classical AQPs (AQP11 and AQP12), which possess unique characteristics.<sup>48</sup> Among these Aquaporins, A comparative analysis revealed diminished AQP3 expression in the colonic tissue of individuals afflicted with diarrhea, while patients experiencing constipation displayed a noteworthy upregulation of AQP3 expression in the colon.<sup>49</sup> The underlying mechanism of AQP3 involves the osmotic pressure differential between the colon lumen and blood vessels, facilitating water transport from the intestinal lumen to the vascular side through AQP3. Elevated levels of AQP3 expression result in excessive water depletion from the intestinal contents, leading to the hardening and accumulation of stools, thereby impeding their passage.

Zhu et al conducted an experimental study aiming to investigate the expression levels of AQP3 mRNA and protein in the colon tissue of constipated mice, which demonstrated an upregulation in the expression levels of both AQP3 mRNA and protein. Subsequently, treatment with *Aloe barbadensis* Mill. led to a significant downregulation in the expression levels of AQP3 mRNA and protein in the colon tissue, ultimately resulting in a decrease in the reabsorption of water in the intestines of the mice.<sup>50</sup>

## Regulation of Intestinal Microbiota by Aloe Barbadensis Mill

The intestinal tract, which is the most densely colonized body part, contains billions of bacteria that strongly influence human health.<sup>51</sup> Interactions between the intestinal flora and the human body encompass the regulation of host immune system development and response, as well as the production of metabolites like short-chain fatty acids (SCFAs), methane and bile acids.<sup>52</sup> These metabolites exert direct or indirect effects on human tissues or target organs, thereby governing the organism's pathophysiological state. The symbiotic relationship between the normal microbiota and the host enhances gut digestion and absorption functions, boosts host immunity, inhibits the growth of pathogenic bacteria, safeguards the intestinal mucosa, and preserves gut microenvironmental homeostasis, ultimately contributing to overall health. Conversely, an imbalance in gut microbial composition, manifests as reduced flora abundance and an increased prevalence of pathogenic bacteria, consequently inducing various chronic diseases, including chronic constipation.<sup>53</sup> The evaluation of intestinal microbial diversity has been extensively explored through quantitative analyses. This investigation primarily relied on conventional microbial culture techniques and the examination of 16S ribosomal RNA (rRNA) gene sequences.<sup>54</sup> Perturbations in the intestinal microbiota of individuals afflicted with constipation manifest as a notable decline in the relative abundance of beneficial bacteria, such as *Lactobacillus*, *Bifidobacterium*, and *Bacteroides spp.*, accompanied by an increase in the relative abundance of potentially pathogenic microorganisms.<sup>55</sup>

In a study conducted by Khalif et al, microbial culture techniques were employed to investigate the gut microbiota of adult patients. The findings revealed a reduced abundance of *Bifidobacterium* and *Lactobacillus* in individuals suffering from constipation compared to the control groups, while there was an observed increase in the levels of *Enterobacteriaceae* and *Staphylococcus aureus*.<sup>56</sup> In a comprehensive exploration of the gastrointestinal microbial composition in human, Mancabelli et al conducted an in-depth analysis of the gastrointestinal microbial composition among individuals with constipation, employing the 16S rRNA sequencing technique alongside whole-genome sequencing methods. The findings unveiled a conspicuous diminishment of *Bacteroides*, *Roseburia*, and *Coprococcus 3* in the gut microbiota of patients.<sup>57</sup> In a parallel cross-sectional pilot study by Zhu et al, employing 16S rRNA gene pyrosequencing, the researchers aimed to elucidate disparities in stool microbial composition between eight constipated individuals and a control group consisting of 14 nonconstipated subjects. The findings from this investigation unveiled a notable decrease in the prevalence of *Prevotella*, accompanied by an increased representation of various genera within the Firmicutes phylum in constipated patients compared to their nonconstipated counterparts.<sup>58</sup> Intestinal flora can influence the propulsion of the gut by affecting the production of SCFAs. The propulsion of gastrointestinal motility can be modulated by the presence of intestinal microbiota, which exerts their influence by regulating the biosynthesis of short-chain fatty acids (SCFAs). These SCFAs, characterized as organic acids consisting of a carbon chain containing fewer than six carbons,<sup>59</sup> are synthesized via the anaerobic bacterial metabolic breakdown of carbohydrates within the colonic environment.<sup>60</sup> Among the SCFAs, acetate, propionate, and butyrate are the most abundant, with acetate comprising approximately 60% of the total SCFAs content, while propionate and butyrate contribute 20% each.<sup>61</sup> Due to the uptake and metabolic processes of SCFAs by colonocytes, especially butyrate, have been primarily associated with colonic functionality, including the regulation of colonic mucosa homeostasis, influence on neuronal excitability, and potential enhancement of the cholinergic-mediated contractile response of the colonic circular muscles *ex vivo*.<sup>62</sup> Therefore, the relationship between gut microbiota and gut transit appears to be bidirectional. In constipation, prolonged colonic transit may facilitate the amplification and colonization of slow-growing species, resulting in significant structural and functional changes throughout the microecology. On the other hand, environmental factors can induce alterations in the gut microbiota, potentially contributing to constipation pathogenesis through microbial metabolic activities.<sup>52</sup>

The impact of Aloe whole leaf extract on bacterial growth and short-chain fatty acids (SCFAs) synthesis was examined in a study conducted by Pogribna et al. The findings revealed that Aloe whole leaf extract exhibited a stimulating effect on the proliferation of three bacterial strains, namely *Bifidobacterium infantis*, *Bacteroides fragilis*, and *Eubacterium limosum*, within a span of 24 hours. Notably, the extent of bacterial growth promotion displayed a positive correlation with the dosage range of Aloe whole leaf extract. Moreover, the inclusion of Aloe whole leaf

extract in the bacterial culture media demonstrated notable alterations in SCFAs profiles. Specifically, the presence of Aloe whole leaf extract led to an augmentation in butyrate production within the *Eubacterium limosum* medium, while an increase in acetate production was observed in the *Bifidobacterium infantis* medium.<sup>63</sup> Ahluwalia et al investigated to examine the impact of *Aloe barbadensis* Mill. intervention on individuals diagnosed with irritable bowel syndrome (IBS), a disorder characterized by alternating occurrences of constipation and diarrhea. The study outcomes revealed a noteworthy augmentation in the abundance of *Akkermansia muciniphila* within the fecal matter, alongside an elevated concentration of butyrate in subjects who demonstrated a favorable response to *Aloe barbadensis* Mill. treatment.<sup>64</sup> These findings suggest the potential of *Aloe barbadensis* Mill. in enhancing the microbial composition and diversity of the gut, thus promoting the establishment of a balanced intestinal microecology in patients.

## ***Aloe barbadensis* Mill. is Used to Treat Various Types of Constipation**

*Aloe barbadensis* Mill. has been acknowledged for its potential therapeutic efficacy in addressing diverse forms of constipation. Its facilitation of intestinal peristalsis serves to expedite the alimentary transit through the digestive tract, concurrently extending the duration of fecal residence in the intestines. Furthermore, the modulation of stool consistency is attributed to *Aloe barbadensis* Mill.'s augmentation of intestinal water content, thereby ameliorating the ease of fecal passage. Consequently, *Aloe barbadensis* Mill. emerges as a viable intervention for a spectrum of constipation conditions, encompassing Stroke bed constipation,<sup>65</sup> Constipation in heroin addicts,<sup>66</sup> Functional constipation in the elderly,<sup>67</sup> Granisetron hydrochloride injection causes constipation,<sup>68</sup> Stroke constipation,<sup>69</sup> Constipation in the large intestine of a horse and mule.<sup>70</sup> Detailed categorizations are presented in Table 1, delineating specific constipation subtypes for comprehensive elucidation.

## ***Aloe barbadensis* Mill. Marketed Products**

In 2021, the total revenue generated by the sales of treatment for constipation drugs in China amounted to approximately \$401 million. Of this, the sales of treatment for constipation drugs containing *Aloe barbadensis* Mill. as the principal constituent were valued at \$126 million, accounting for 31.34% of the overall sales. Due to its recognized gastroprotective and immunoregulatory properties, *Aloe barbadensis* Mill. has garnered attention as a potential candidate for therapeutic applications. Numerous commercially available products have employed *Aloe barbadensis* Mill. as a vital ingredient, inspiring researchers to evaluate its efficacy in treating constipation. To gain a deeper understanding of the effectiveness of this botanical remedy, scholars have analyzed commercially available *Aloe barbadensis* Mill. preparations. Here are a few products that have been marketed for the treatment of constipation with *Aloe barbadensis* Mill. (Table 2).

## ***Aloe barbadensis* Mill. Mono-Preparation**

### ***Aloe Barbadensis* Mill. Soft Capsule**

*Aloe barbadensis* Mill. soft gels, a traditional mono-preparation, exhibit satisfactory efficacy in treating constipation with a low daily cost of approximately \$0.18 for patients. In this study, Hu investigated the treatment for the constipation function of *Aloe barbadensis* Mill. soft gels by treating constipated mice with varying doses of the capsule's contents. The results indicated that the 0.800 g/kg dose of *Aloe barbadensis* Mill. soft capsule significantly increased the rate of

**Table 1** Types of Constipation Treated with *Aloe Barbadensis* Mill

Constipation Type	Dosage Form	Course of Treatment
Stroke bed constipation	Suppository	Three weeks
Constipation in heroin addicts	Capsule	One week
Functional constipation in the elderly	Capsule	One week
Granisetron hydrochloride injection causes constipation	Capsule	Five days
Stroke constipation	Enema Solution	One day
Constipation in the large intestine of a horse and mule	Sugar Solution	One day

**Table 2** Composition of Some *Aloe barbadensis* Mill. Products and Daily Cost

Category	Name	Main Components	Daily Dose	Cost/Day
<i>Aloe barbadensis</i> Mill. mono-preparation	<i>Aloe barbadensis</i> Mill. Soft Capsule	<i>Aloe barbadensis</i> Mill.	1 g /qd	\$0.17
	<i>Aloe barbadensis</i> Mill. Capsule	<i>Aloe barbadensis</i> Mill.	0.6 g /qd	\$0.24
	<i>Aloe barbadensis</i> Mill. Navel Paste	<i>Aloe barbadensis</i> Mill.; Ethanol	N/A	N/A
<i>Aloe barbadensis</i> Mill. compounding	<i>Aloe barbadensis</i> Mill. Pearl Capsule	<i>Aloe barbadensis</i> Mill.; Pearl; <i>Saussurea costus</i>	1 g /bid	\$0.23
	Xin Fufang Luhui Capsule	<i>Aloe barbadensis</i> Mill.; Indigo Naturalis; Amber	0.86 g/qd	\$0.26
	Shouhui Tongbian Capsule	<i>Aloe barbadensis</i> Mill.; <i>Fallopia multiflora</i> ; <i>Colla corii asini</i> ; Ginseng	0.7 g /tid	\$7.8

small intestine ink advancement, reduced the time to defecate the first black stool, and increased the number of defecations in constipated mice, without inducing diarrhea. Additionally, Hu conducted a clinical trial involving 102 voluntary subjects to assess the efficacy and safety of *Aloe barbadensis* Mill. soft capsules in treating constipation. Patients in the experimental group received *Aloe barbadensis* Mill. soft capsules for 7 days, while the control group received a placebo. The results of the study showed that the number of bowel movements in the experimental group increased significantly before and after taking the drug, the stool characteristics were improved, and the total effective rate of taking the drug was 76.47%. Furthermore, the experimental group demonstrated significantly improved bowel movements and stool characteristics compared to the control group after taking the drug, and no adverse reactions or safety concerns were observed in the experimental group.<sup>71</sup> These results suggest that *Aloe barbadensis* Mill. soft capsules may be an effective and safe option for treating constipation.

**Aloe Barbadensis Mill. Capsule**

*Aloe barbadensis* Mill. capsule stand as a prominent Chinese herbal therapeutic intervention, celebrated for their notable effectiveness in the mitigation of constipation, accompanied by a cost-effective daily expenditure of merely \$0.24 per patient. This herbal remedy has garnered recognition within the realm of traditional Chinese medicine for its commendable outcomes in constipation treatment. Qu et al conducted an investigation involving 60 individuals afflicted with annular mixed hemorrhoids during their postoperative phase. The administration of *Aloe barbadensis* Mill. capsules yielded substantial improvements in the difficulty of defecation, fecal characteristics, and defecation duration among postoperative mixed hemorrhoid patients. Impressively, the overall treatment efficacy reached 95%.<sup>72</sup> In a separate investigation by Ye et al, 50 elderly patients grappling with functional constipation were meticulously examined. The protocol involved the oral intake of 2 *Aloe barbadensis* Mill. capsules prior to bedtime. The findings indicated notable amelioration in 31 patients, with minimal adverse reactions observed during the treatment course.<sup>73</sup> These adverse events were limited to a subset of patients experiencing diarrhea and abdominal discomfort. Importantly, these side effects were effectively managed and resolved promptly through appropriate interventions. These studies collectively underscore the promising therapeutic potential of *Aloe barbadensis* Mill. capsules in addressing constipation-related issues, serving as a cost-effective and well-tolerated intervention.

**Aloe Barbadensis Mill. Navel Paste**

*Aloe barbadensis* Mill. can be administered orally for the treatment of constipation, and it also offers potential for external application in the management of constipation. Because of the rich capillaries distributed on both sides of the navel, the application of *Aloe barbadensis* Mill. here is conducive to long time storage and penetration of drugs, plus the pungent and warm effect of ethanol, which makes the blood vessels dilate and facilitate the penetration of *Aloe*

*barbadensis* Mill. into the large intestine, stimulating the wall of the large intestine to cause intestinal contraction and increased secretion of water and fluid to achieve treatment for constipation purposes. Zhang et al carried out a randomized controlled trial on a sample of 118 individuals aged between 19 and 63 years with constipation. Participants were allocated into test and control groups using both self-control and between-group control designs. The test group was administered *Aloe barbadensis* Mill. soft gels, while the control group was given placebo capsules. After seven consecutive days of the administration, the frequency of bowel movements was measured. The findings revealed that the test group experienced a statistically significant increase in bowel movements in comparison to their pre-intervention levels, and also had a significantly higher number of bowel movements than the control group. Simultaneously, this approach circumvents the potential adverse effects arising from the co-administration of oral treatment for constipation and antipsychotic medications within the gastrointestinal tract, thereby introducing a novel avenue for managing pharmacological constipation.<sup>74</sup>

## Aloe barbadensis Mill. Compounding

### Aloe Barbadensis Mill. Pearl Capsule

The aloe pearl capsules consisting of *Aloe barbadensis* Mill., *pearls*, and *Saussurea costus*. Wang et al conducted a study to investigate the effects of the capsule on intestinal peristalsis. The results indicated demonstrated that this particular intervention led to significant enhancements in both the amplitude and frequency of intestinal muscle contractions in rabbits.<sup>75</sup> Meanwhile, Liu selected a cohort of 82 patients diagnosed with myocardial infarction and presenting with constipation symptoms. The patients were divided into two groups, a control group consisting of 41 individuals who underwent conventional treatment, and an experimental group of 41 patients who were administered the capsule. The results demonstrated that the treatment efficacy in the experimental group was observed in 39 patients (95.12%), whereas in the control group, it was observed in 28 patients (68.29%). Therefore, the findings of this study suggest that the capsule could be an effective treatment option for patients with myocardial infarction and constipation symptoms.<sup>76</sup> In terms of pharmacoeconomics, the capsules in question are deemed cost-effective and readily accessible, with a daily cost of approximately \$0.23.

### Xin Fufang Luhui Capsule

Xin Fufang Luhui Capsule is composed of *Aloe barbadensis* Mill., *Indigo Naturalis* and *Amber*. Gong's investigation focused on the potential treatment for constipation properties of the capsules on mice in three distinct constipation models. The study showed that administration of the capsule significantly increased defecation frequency and the number of pellets expelled within 8 hours, while also enhancing small bowel propulsion in mice with gastrointestinal motility disorders. Additionally, a clinical trial was conducted with 224 participants, divided into two groups receiving either the capsule or a placebo, taken twice daily for a week. The study results indicated that the capsules elicited a significant treatment for constipation effect compared to the placebo group, and remained effective for up to one week after discontinuation.<sup>77</sup> From a pharmacoeconomic perspective, the capsule presents an advantage in terms of ease of administration and affordability, with a minimal daily treatment expense of \$0.26.

### Shouhui Tongbian Capsule (SHTC)

The encapsulated therapeutic regimen for ameliorating constipation comprises a proprietary blend of eight traditional Chinese botanical constituents, with particular emphasis on the principal constituent, *Aloe barbadensis* Mill. and *Fallopia multiflora*. Lin et al employed loperamide to establish a functional constipation model in rats, characterized by delayed gut transmission. The experimental groups consisted of the normal control group (NC), the Shouhui tongbian capsule group (SH), the loperamide HCl model group (LOP), the bisacodyl enteric-coated tablets positive group (BE), the low Shouhui tongbian capsule dose group (LS), and the high Shouhui tongbian capsule dose group (HS). The findings of this investigation provide evidence supporting the therapeutic effects of SHTC on constipation induced by loperamide. Administration of SHTC demonstrated notable amelioration in key physiological parameters including body weight, gastric emptying rate, and fecal moisture content. Additionally, SHTC treatment exhibited a significant mitigating effect on the histopathological alterations in the small intestine associated with constipation.



Notably, SHTC-treated constipated rats displayed a remarkable elevation in the levels of acetic acid and propionic acid, both recognized as short-chain fatty acids (SCFAs), thereby emphasizing the potential biochemical impact of SHTC in the modulation of gut microbiota.<sup>78</sup> Meanwhile, Lu et al conducted a study to investigate the efficacy and safety of the capsule in the treatment of functional constipation. The study population consisted of 2396 patients, who were categorized into three age groups: 18–40 years ( $n = 683$ ), 41–60 years ( $n = 1018$ ), and 61 years and above ( $n = 695$ ). The researchers observed improvements in bowel movement frequency, difficulty, and duration in all age groups, indicating the effectiveness of the capsules in treating functional constipation across different age groups. Furthermore, the capsules were found to be safe as no significant adverse effects were observed in any of the groups. Notably, the study results showed that the capsules were more effective in younger patients.<sup>79</sup> From a pharmacoeconomic perspective, these capsule exhibits enhanced efficacy but also entails increased expenses for the treatment of constipation, with a daily cost of approximately \$7.80.

## Toxicology of *Aloe barbadensis* Mill

*Aloe barbadensis* Mill. emerges as a comparatively safe category of therapeutic agents for constipation, demonstrating limited documented toxic side effects. Notably, reported clinical instances of toxicity predominantly implicate the kidneys, and the frequency of such events appears correlated with the source of extraction of *Aloe barbadensis* Mill. Extract. In this study, Florence et al aimed to assess the acute toxicity of *Aloe barbadensis* Mill. green rind extract and *Aloe barbadensis* Mill. whole leaf extract in Wistar albino rats via 28 days of gavage administration at 200, 400, and 800 mg/kg dosages. Through examination of photomicrographs, the researchers observed mild necrosis in the kidneys of rats treated with *Aloe barbadensis* Mill. green rind extract. However, some rats treated with 200 and 800 mg/kg of *Aloe barbadensis* Mill. whole leaf extract exhibited inflammation of the renal interstitium.<sup>80</sup> The above experiments were conducted to investigate the acute toxicity of *Aloe barbadensis* Mill., and the dose used was relatively high, which inevitably led to toxic side effects, however, such a high dose was not necessary in the use of *Aloe barbadensis* Mill. for constipation, thus to explore the toxicity of *Aloe barbadensis* Mill. in the treatment of constipation, Wintola et al administered aqueous extracts of whole leaves of *Aloe barbadensis* Mill. to rats with loperamide-induced constipation at varying doses of 50, 100 and 200 mg/kg. The effects of the extract on the hematological parameters as well as hepatic and renal functional indices of the rats were evaluated. The results indicate that the extract did not cause any significant adverse effects on the kidney and liver or the indicators of renal function including serum creatinine, uric acid, urea, calcium, and potassium ions levels at all studied doses. Moreover, the extract was able to restore alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) to normal levels in constipated rats after treatment with *Aloe barbadensis* Mill.<sup>81</sup> Based on the available evidence, the study suggests that *Aloe barbadensis* Mill. is safe for oral administration in the treatment of constipation. Whilst *Aloe barbadensis* Mill. is generally deemed to be safe, several adverse reactions have been reported in its use as a treatment for constipation. One such reaction is Melanosis coli (MC), which represents a noninflammatory bowel condition characterized by the deposition of brown or black pigment within the colorectal mucosa.<sup>82</sup> The incidence rates of MC fall within a range of roughly 0.82% to 1.13%.<sup>83</sup> It is typically caused by prolonged use of anthraquinone treatment for constipation, including senna, rhubarb, and *Aloe barbadensis* Mill. MC tends to occur more frequently in individuals with chronic constipation and is generally a benign and reversible condition that gradually resolves within a few months following the cessation of treatment for constipation use, as the patient's colon returns to normal.<sup>84</sup> Overall, the safety of *Aloe barbadensis* Mill. as a treatment for constipation is considered to be dependable in the current scientific discourse.

## Conclusions

The field of constipation exhibits promising market potential, with historical evidence of *Aloe barbadensis* Mill. utilization in constipation management tracing back over 4000 years. Capitalizing on recent advancements in scientific and technological research, a prospect pathway emerges for further investigation into the active constituents and molecular mechanisms underlying *Aloe barbadensis* Mill. 's therapeutic effects. By harnessing state-of-the-art techniques, the exploration of this extraordinary herb presents a distinctive prospect to unravel the latent therapeutic capacity in the context of constipation treatment. Simultaneously, the integration of modern technology promises to

unveil additional enigmas surrounding *Aloe barbadensis* Mill., thereby amplifying its intrinsic value in the domain of constipation therapy.

## Abbreviations

ALT, Alanine aminotransferase; ALP, Alkaline phosphatase; AQPs, Aquaporins; CFTR, Cystic Fibrosis Transmembrane Conductance Regulator; ENS, Enteric nervous system; GDNF, Glial cell-derived neurotrophic factor; ICC, Interstitial cells of Cajal; MC, Melanosis coli; NO, Nitric oxide; SCF, Stem cell factor; SCFAs, Short-chain fatty acids; sCG, soluble guanylyl cyclase; SHTC, Shouhui tongbian Capsule; SP, Substance P; VIP, Vasoactive peptide.

## Data Sharing Statement

The data used to support the findings of this study are included in the article.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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