

**Review Article****Medicinal Plants with Spasmolytic Activity for Treating Infantile Colic**Samane Jahanabadi^{1,2}, Abood Ul Haq³, Hiba Imran^{*4}¹Department of Pharmacology and Toxicology, Faculty of Pharmacy, Shahid Sadoughi University of Medical Sciences Yazd Iran.²Pharmaceutical Science Research Center, Shahid Sadoughi University of Medical Sciences Yazd, Iran.³Shoppers Drug Mart, Calgary, Canada⁴PMAS-Arid Agriculture University Rawalpindi, Pakistan*Correspondence: hibaimran280@gmail.com

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Abstract

Colic is a multifaceted ailment with a wide range of therapeutic strategies. Infantile colic is often regarded as the most excruciating agony a newborn has ever experienced. Inconsolable crying, fussing, irritability, and abdominal discomfort are some of the classical presentations of infantile colic. In addition, infantile colic is associated with various gastrointestinal conditions and behavioral and neurodevelopmental complications. Although there is inadequate data to support successful treatment for infantile colic, a few frequently applied pharmaceutical interventions, such as dicyclomine, simethicone, and cimetropium, have not been recommended based on contemporary research. Lifestyle modifications such as lactase and probiotics supplements have indicated benefits in treating colic, but additional control studies will be a prerequisite to assess their efficacy. This review aims to provide in-depth information on colic, its pathophysiology, the therapeutic potential of medicinal plants with spasmolytic effects, and their possible mechanisms of action. Studies on several medicinal plants with spasmolytic activity, like *Foeniculum vulgare*, *Carum carvi*, *Matricaria chamomilla*, *Zingiber roseum*, *Lavandula angustifolia*, and *Mentha pulegium* have been included in this article. Furthermore, the study showed that the active compounds in these plants have a substantial antispasmodic activity that is safer and more effective than currently accessible synthetic medications.

Keywords: Colic, pathophysiology, treatment, medicinal plants, spasmolytic activity.**1. Introduction**

Colic represents one of the most common problems affecting neonates in most world countries. Colic is detailed as inexplicable bouts of irritation, fussing, and crying spanning 3 hours a day for 3 days per week in a healthy infant of 2 weeks to 4 months (Wessel et al. 1954). Rome diagnostic criteria III demarcated infantile colic (IC) as a functional gastrointestinal disease (van Tilburg et al. 2016). Infant colic occurs when the crying of a healthy baby becomes chronic, distraught, intense, and inexplicable. Even though infantile colic is a typically self-limiting ailment, it causes significant discomfort for the newborn, parents, family, and medical providers (Keefe 2004). The intense crying of most neonates resolves instinctively by 4 months of age

(Parkin, Schwartz, and Manuel 1993). Nevertheless, the consequences of infantile colic on the child's development or the family dynamics may endure and have a detrimental effect on both the baby and the family. Colic is closely linked to maternal depression (Vik et al. 2009) and is the most important contributing factor to shaken baby syndrome (Sung 2018).

The incidence of IC varies greatly. IC occurrence varied from 17-25% during the initial 6 weeks of life. These rates lowered to 11% and 0.6% at 8 weeks and 10 weeks of infancy, respectively (Wolke, Bilgin, and Samara 2017, Chogle et al. 2016). There seem to be no disparities in colic prevalence rates between boys and girls (Lucassen et al. 2001) or between breastfed and formula-fed infants (Clifford et al. 2002). IC is expressed

by its chronic, distressed, and inexplicable characteristics (Benninga et al. 2016). Colic's typical features include face flushing, crying, fist clenching, abdominal discomfort, and painful bowel movements (Illingworth 1985). Colicky neonates typically exhibit symptoms such as excessive flatulence and constant crying. They are intensely distressed and bad-tempered and tend to draw their knees towards their abdomen when they are in discomfort. The peak of colic manifestation is around 6-8 weeks postpartum (Iacovou et al. 2012). The period of crying bouts in IC is linked to caretaker dissatisfaction (Fujiwara et al. 2011). Moreover, one investigation discovered that babies suffering from colic cry at a greater frequency and sound coarser than babies without colic (Lester et al. 1992). Contrarily, some studies have revealed no differences in dysphonation and frequency between colicky and non-colicky infants (Zeskind and Barr 1997).

2. Pathophysiology

Regardless of years of research, the pathogenesis of infant colic is still anonymous. Presently, babies with IC are occasionally referred to pediatric

gastroenterologists because parents typically believe that crying denotes stomach pain of gastrointestinal cause (Benninga et al. 2016, Hyman et al. 2006). Nonetheless, whether the gastrointestinal system prompts IC is ambiguous (Shamir et al. 2013). IC can be viewed as an intensification of a normal infant's behavior triggered by a combination of physiological and psychosocial causes that are covered in Table 1 (Barr 1998).

2.1. Fecal Microbiota

It is indicated that fecal specimens from colicky infants may vary in respect of *Lactobacillus spp.* abundance. For instance, feces from colicky babies included only *Lactobacillus lactis* and *Lactobacillus brevis*, but those from non-colicky babies had solely *Lactobacillus acidophilus* (Savino, Bailo, et al. 2005). However, the exact impact of *Lactobacillus spp.* in the progress of IC is obscure. The relative abundance of bacteria from *Klebsiella* and *Escherichia* genera is reported to be higher in fecal samples from colicky babies. Research has also discovered that colicky babies had elevated amounts of fecal calprotectin, which is a biomarker of intestinal inflammation (Rhoads et al. 2009, Savino et al. 2009).

Altered Intestinal Microflora

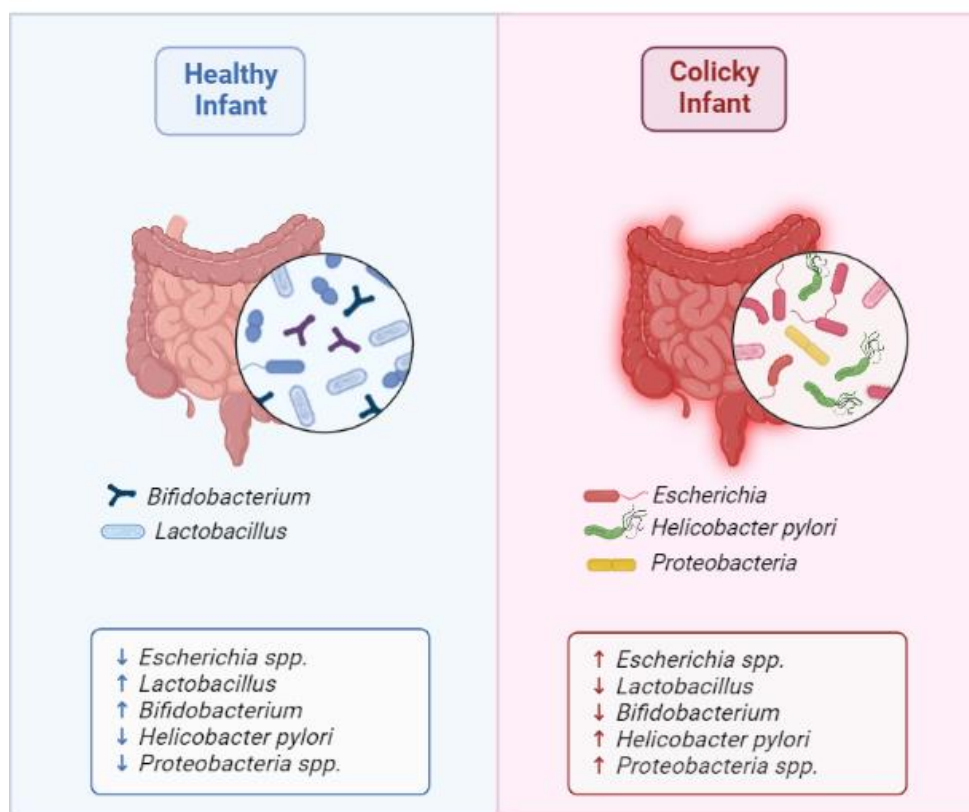


Figure 1 Variation in the microbiome of the gut in the normal and colicky infant.

2.2. Altered Gut Microbiome

Current findings have revealed that colicky infants have definite microbial profiles. Gram-negative microbes, such as *Escherichia spp.*, have been confirmed to be more widespread in colicky infants than in non-colicky infants. The high concentration of *Escherichia spp.* can induce intensified intestinal discomfort and elucidate immoderate crying in colic neonates (Rhoads et al. 2009, de Weerth, Fuentes, and de Vos 2013). During the first 2 weeks after birth, colicky infants' microbiome showed lower numbers of *Lactobacillus* and *Bifidobacterium* than the microbiome of non-colicky infants. Additional research indicated that habitation of *Proteobacteria spp.* in the gut was connected with greater crying in babies as young as 3 months old. Furthermore, at 2 to 4 weeks of age, variations in the

abundance of the genera *Vibrio*, *Pseudomonas*, *Yersinia*, and *Serratia* were detected in colicky babies compared to non-colicky babies. Studies performed in 3 different countries revealed that *Helicobacter pylori* were considerably more abundant in the intestine in colicky babies than in non-colicky babies (de Weerth, Fuentes, and de Vos 2013, Ali 2012, Ali and Borei 2013). Different bacterial species that are altered in the gut microbiota of colicky infants are indicated in Figure 1.

2.3. Gas Production

A large volume of gas production in the intestine in colicky infants can be induced by the fermentation of dietary carbohydrates, e.g., lactose. It is a key process in colic disease (Savino et al. 2017, Savino et al. 2009). IC colic symptoms are relieved once the gas is passed (Treem 1994).

Table 1: Possible gastrointestinal and non-gastrointestinal factors contributing to the pathophysiology of IC

Causes	Factors	Possible mechanism	Ref
Gastrointestinal	• Lactose intolerance	Malabsorption of lactose due to lactase enzyme deficiency.	(Kanabar, Randhawa, and Clayton 2001)
	• Variation of the gut microbiome	High no. of <i>Proteobacteria</i> , low no. of <i>Lactobacillus</i> and <i>Bifidobacteria</i> .	(Savino, Bailo, et al. 2005)
	• Fluctuation of gut hormone	Increased motilin & ghrelin hormone triggering distressed GI motility, discomfort, and hyperperistalsis.	(Savino et al. 2006)
	• Sensitivity to cow's milk protein	Allergic reactions after drinking cow milk protein. Impairment of the GIT lining.	(Hill and Hosking 2000)
	• Excessive intestinal gas	Partial absorption of carbohydrates in the intestine, followed by fermentation, which can be allied with intestinal immaturity.	(Moore, Robb, and Davidson 1988)
Non-Gastrointestinal	• Behavioral causes	Suboptimal interaction between parent and infant can cause insecure attachment, which may lead to colic.	(Akman et al. 2006)
	• Psychological factors	Infants can sense maternal anxiety and depression.	(Paradise 1966)
	• Immaturity of the ENS	Stress, infections, and nutrition can significantly modify ENS.	(Camilleri et al. 2017)
	• Improper feeding	Poor responsiveness during feeding may lead to underfeeding, overfeeding, swallowing air, or not being adequately burped, which can result in colic.	(Miller-Loncar et al. 2004)
	• An early form of migraine	Maternal migraine can present an early-life manifestation of migraine in colicky infants due to genetics.	(Gelfand 2016)
	• Maternal smoking	Maternal smoking during pregnancy can cause increased blood motilin concentration that may predispose infants to colic.	(Canivet et al. 2008)

2.4. Gut Dysmotility

In conjunction with the abnormal mucus secretion, gut dysmotility may affect the gut habitat in which bacteria live. The modified gastrointestinal environment may impact microbial ecology, perhaps leading to infant colic (Dinan and Cryan 2012). Besides, the enteric nervous system (ENS) delimits peristalsis in the GI tract. Momentary disturbance of this nervous system during infancy may cause hyper-peristalsis in colic babies, mainly during the first few weeks of life.

2.5. Neurodevelopmental Behavior

A neurodevelopmental rationale has been theorized for the occurrence of IC (James-Roberts, Alvarez, and Hovish 2013). Following a neurobehavioral consideration, IC was related to aggravated crying and inconsolable discomfort (St James-Roberts et al. 2003). In addition, mother-infant interactions, mother anxiety, and depression, and infant temperament might also have a role in colic (Hiscock and Jordan 2004, R  ih   et al. 2002).

2.6. Microbiota-Gut-Brain Axis

A study has indicated a linkage between IC and immaturity of the ENS, inflammation of the gut, dysbiosis, and irregular production and regulation of bile acid, all of which is aided by the microbiota-gut-brain axis (de Weerth, Fuentes, and de Vos 2013, P  rtty et al. 2017, Camilleri et al. 2017). Mechanisms that are associated with the gut-brain axis are shown in Figure 2.

2.7. Intestinal Dysbiosis

Concerning microbial diversity, stability, and colonization behaviors, the gut microbial identities of babies with colic vary from those of babies without colic (de Weerth et al. 2013). These variations recommended that intestinal dysbiosis may have a function in the manifestation of IC symptoms (Dryl and Szajewska 2018). In addition, intestinal dysbiosis can impair enteric and central neural function, including pain sensing in babies (Mayer, Tillisch, and Gupta 2015, de Weerth, Fuentes, and de Vos 2013), which might contribute to excessive crying (Eutam  ne et al. 2017).

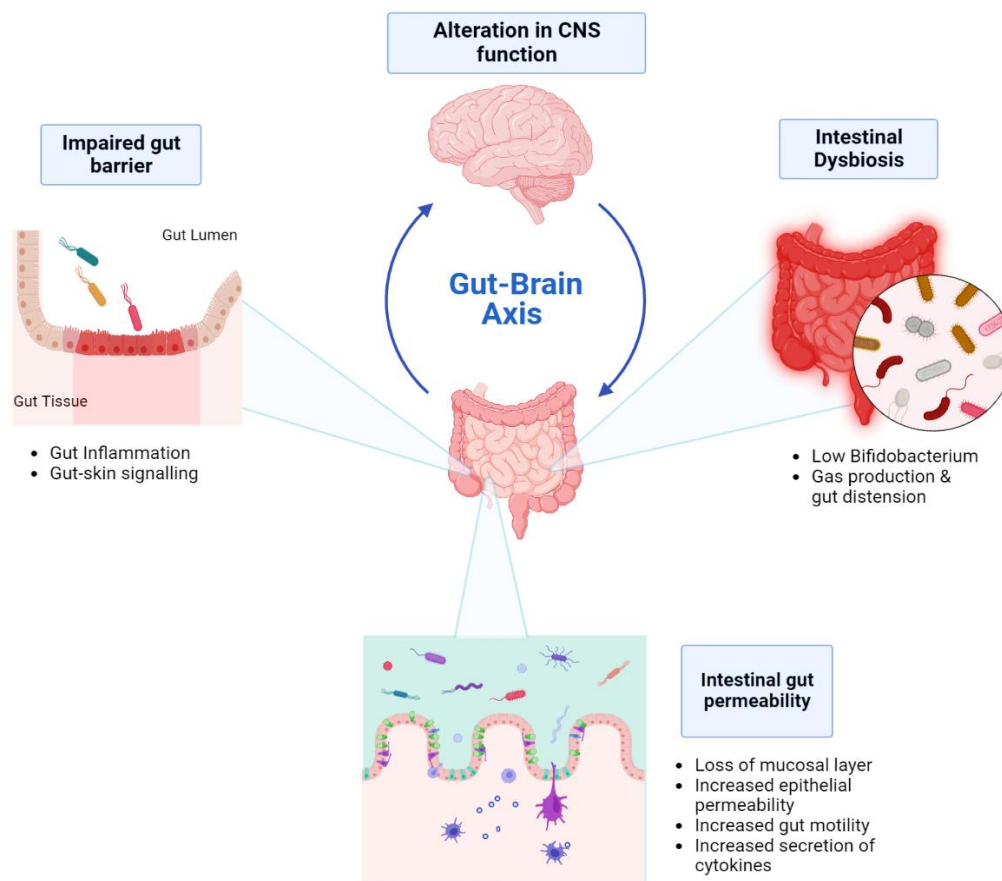


Figure 2 Possible mechanisms through which Gut-Brain Axis can contribute to colic.

2.8. Gut Inflammation

Gut inflammation seems to be another potential cause. A recent study demonstrated that colicky infants expressed amplified numbers of pro-inflammatory cytokines and chemokines in their blood than non-colicky infants (Pärty et al. 2017). In addition, gram-negative microbes, for instance, *Bacteroidetes* and *Escherichia* can trigger intestinal inflammation by expressing lipopolysaccharides on their outer surface and may therefore be pathogenically concomitant with colic (Vatanen et al. 2016). Nonetheless, it is questionable whether gut microbiome variations in colicky infants promote inflammation of the gut or whether they are the outcome of inflammation of the gut (Pärty et al. 2017, Rhoads et al. 2009). Increased gut permeability and abdominal hypersensitivity are two additional putative mechanisms coupling these microbial profiles to excessive crying (Eutamène et al. 2017).

2.9. Bile Acid Synthesis

Aside from bacterial colonization processes, an additional aspect suggested to indirectly produce IC is the pathophysiology of bile acid synthesis during the initial 6-8 weeks of life. Declined intraluminal concentration of bile acids in the baby's gut might culminate in the malabsorption of nutrients and fat, which may influence IC (Camilleri et al. 2017). In adolescents, decreased bile acid combined with high levels of short- and long-chain fatty acids can cause painful colonic spasms (Bampton et al. 2002, Spiller, Brown, and Phillips 1986) that can be linked to pain (Camilleri et al. 2017).

2.10. Immaturity of the ENS

Immaturity of the ENS, which promotes aberrant gastrointestinal motility and sensory functioning, is a component that may have an indirect influence on IC (Camilleri et al. 2017). The ENS, in conjunction with exogenous innervation, regulates gut motility and mucus secretion (Wood 2008). It is presumed that as the nervous system and the gut are undeveloped in infants, air remains curbed in the colon, causing straining of the bowel and thus leading to colic disease.

3. Conventional Treatment

The treatment of colic relies on the theoretical cause of colic. When no worrisome signs or symptoms are observed, colic should be dealt with empathy and reassurance. Multiple therapeutic approaches for newborn colic have already been proposed.

Unfortunately, notwithstanding decades of study, effective colic care options are sparse. Typically, treatment is tailored to the individual, focusing on educating parents on the benign character of the disease and addressing their feelings of inadequacy. This section provides a brief overview of the potential treatment modalities and the evidence supporting their efficacy in colic. Lactase supplements, antispasmodics, probiotics, and chiropractic techniques are various recommended treatment options (Figure 3) (Dobson et al. 2012, Biagioli et al. 2016).

Probiotics have been considered a possible therapeutic option for colic because recent research shows that the gut microflora plays a function in the progression of IC (de Weerth et al. 2013, Harb et al. 2016). Specifically, *L. reuteri* DSM 17938 is the frequently utilized probiotic in colicky infants (Dryl and Szajewska 2018). Baby massage can be helpful for colicky newborns because it strengthens the formative bond between mother and baby and offers sensory stimulation, which induces pacifying effects in babies (White-Traut and Nelson 1988, Brackbill 1973). According to a comprehensive review, limiting cow milk from the mother's diet is useful in curing IC. In formula-fed babies with colic, hydrolysate formulations are beneficial in alleviating crying episodes (Iacovou et al. 2012, Hall, Chesters, and Robinson 2012).

Two anticholinergic drugs, dicyclomine and cimetropium are employed to treat colic premised on the etiological concept that pain in the intestine is caused by immature ENS, which causes intestinal spasms. These drugs minimize the hours of crying (Hall, Chesters, and Robinson 2012, Lucassen et al. 1998). Furthermore, cimetropium and dicyclomine induce smooth muscle relaxation by acting on the cholinergic receptors, respectively (Moore et al. 2003). Simethicone was also used to treat colic but has very low effectiveness and is not endorsed now (Savino et al. 2014). Lastly, oral sucrose solution has been ascertained to have calming and analgesic effects on neonates (Carbajal et al. 1999).

4. Problems with Conventional Treatment

Anticholinergic drugs should not be used frequently for the treatment of colic, given the mounting evidence of their dire outcomes, including an elevated likelihood of infection (Gordon et al. 2018). Dicyclomine was noticeably superior to a placebo for the intervention of colic, but it is not recommended for babies younger than 6 months old due to its detrimental effects.

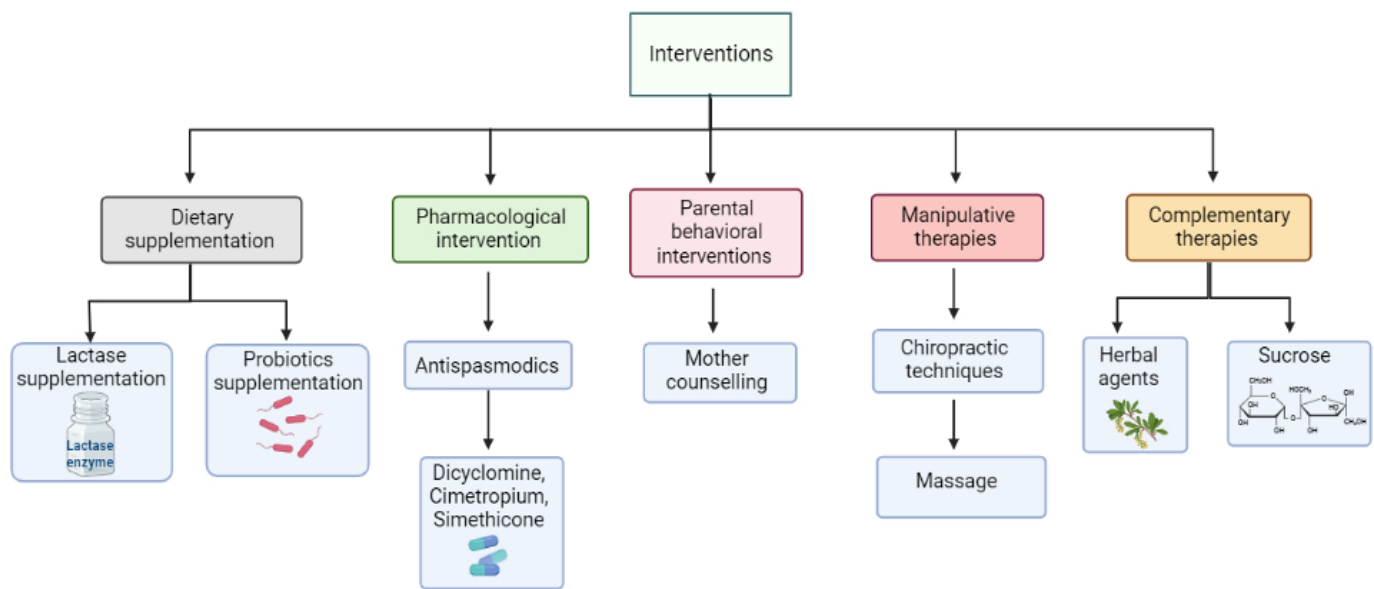


Figure 3: Treatment options for infantile colic.

Respiratory difficulty is one of the side effects of using dicyclomine. As stated by the manufacturer, trouble sitting upright, constipation, diarrhea, drowsiness, and coma are dicyclomine's adverse effects. Death occurs in 5% of infants who received dicyclomine hydrochloride treatment. Additionally, two babies were noted to have experienced brief episodes of temporal cessation of breathing (Garrison and Christakis 2000, Williams and Watkins-Jones 1984).

Though simethicone drops are widely accessible and routinely used to manage colic, a detailed assessment of three research indicated that they are not superior to a placebo (Garrison and Christakis 2000). First, cimetropium bromide reduces the length of crying tremendously but has low efficacy and does not reduce the number of cries in compliance with symptomatic features (Savino et al. 2014). Furthermore, cimetropium and sucrose had insufficient supporting data for their efficacy in colic. As a result, it was deemed that no recommendations could be given about the efficiency of painkillers for treating colic (Biagioli et al. 2016).

5. Remedies From Natural Sources

Herbal medicines have several applications and are used to treat and manage a variety of illnesses. Various parts of medicinal plants are frequently employed in the treatment of gastrointestinal diseases due to their spasmolytic effects (Table 2). Antispasmodic

compounds are widely dispersed in nature. In this section, we discussed contemporary information on 13 medicinal plants with a spasmolytic effect that could be utilized to treat colic.

5.1. *Foeniculum vulgare*

F. vulgare (fennel) suppresses gastrointestinal fermentation and has anti-flatulent and antispasmodic effects (Westphal, Hörning, and Leonhardt 1996, Lis-Balchin and Hart 1997). A fennel seed extract has been proven to minimize intestinal spasms and accelerate small intestine motility. Another research on the impact of fennel seed oil in minimizing colic pain in neonates revealed that fennel minimizes colic pain and the rate of crying hours in colicky babies. Fennel oil emulsion application eradicated colic in 65% of the colicky babies, and no adverse effects were evident in this study (Alexandrovich et al. 2003). One research concluded that fennel tea could substantially reduce crying hours when compared to routine care (Arikan et al. 2008). Additionally, research showed that an emulsion of 0.1% of fennel seed extract provides substantial relief in colic symptoms and crying hours with low side effects as compared to a placebo (Alexandrovich et al. 2003).

5.2. *Carum carvi*

C. carvi (caraway) has previously been used as a spice in meals and beverages and a natural herb for gastrointestinal diseases such as dyspepsia and other spasmodic disorders, bloating, diarrhea, and flatulent

colic (Johri 2011). Although caraway essential oil is not intended for people under the age of 18 because of a lack of scientific data, it can be employed topically as a carminative and antispasmodic agent for IC. For example, caraway oil is mixed with olive oil and can be directly massaged onto the baby's abdomen to promote digestive function and relieve colic (Peter 2006). Additionally, ethanolic extract of *C. carvi* (2.5 mg/mL) was reported to have antispasmodic activity on the intestinal smooth muscle cells of the guinea pig (Al-Essa et al. 2010).

5.3. *Mentha piperita*

Mentha piperita (peppermint) is an effective herb employed to treat various symptoms and ailments (Keifer et al. 2007). It is used in both medicinal preparations and to flavor food. *M. piperita* has antispasmodic activity on gastrointestinal smooth muscle (Taylor, Luscombe, and Duthie 1983). Scientific data inferred that *M. piperita* liquid drops might be helpful in the elimination of IC. The study reported a reduction in the length and frequency of IC symptoms. Nonetheless, there were no distinctions in *M. piperita* and simethicone responsiveness (Alves, de Brito Rde, and Cavalcanti 2012).

5.4. *Zingiber roseum*

In rat duodenum smooth muscle, *Zingiber roseum* seed oil was reported to have a dual effect (contraction and relaxation) as well as an antispasmodic activity. The *Z. roseum* seed oil was powerful enough to induce its effect in $\mu\text{g/ml}$ dose ranges. *Z. roseum* seed oil dual response was an indicator of the existence of two independent mechanisms by which it performs its spasmolytic effects (Prakash et al. 2006b).

5.5. *Atropa belladonna*

A. belladonna (deadly nightshade or belladonna) is a poisonous herb. *A. belladonna* possesses alkaloids in its roots and leaves, for instance, atropine, hyoscyamine, and scopolamine. *A. belladonna* is utilized in both homeopathic and allopathic medicine. In allopathy, atropine, and scopolamine induce spasmolytic activity, which aids in treating colic. They inhibit muscarinic receptors, thus inducing smooth muscle relaxation. Scopolamine is marked as a more effective antispasmodic than atropine (Clissold and Heel 1985, Izaddoost and Robinson 1987). Atropine is an eminent anticholinergic chemical in belladonna. Atropine's antagonistic activity on muscarinic receptors causes gastrointestinal muscle relaxation, relieving spasms and inhibiting diarrhea.

5.6. *Fumaria officinalis*

Fumaria officinalis (common fumitory) is a popular herb abundant in phytotherapeutic agents. The findings of an investigation demonstrated that *F. officinalis* had an antispasmodic action on the gastrointestinal tract (Hentschel, Dressler, and Hahn 1995). Fumaria extract, which has spasmolytic properties (Gilani et al. 2005), is an inexpensive medicine that can substantially alleviate colic symptoms in babies aged 3 to 16 weeks (Montaseri, Pourarian, and Montaseri 2013). Furthermore, assessing the effect of common fumitory and other similar herbal remedies reveals that common fumitory has greater benefits in minimizing the length and frequency of crying as well as the event of awakening in newborns than herbal tea containing licorice, vervain, lemon balm, and chamomile (Crotteau, Wright, and Eglash 2006).

5.7. *Melissa officinalis*

Melissa officinalis (lemon balm) exhibits an antispasmodic effect on intestinal smooth muscle since it contains flavonoid ingredients and essential oil, particularly apigenin (Soulimani et al. 1991). *M. officinalis* is widely recognized for its anti-inflammatory qualities, as well as its sedative and anxiolytic characteristics. In an experimental model, the antispasmodic effect of *M. officinalis* induced the relaxation of the intestinal muscles (Avallone et al. 1996).

5.8. *Lavandula angustifolia*

A researcher reported that aromatherapy massage with *Lavandula angustifolia* (lavender) oil might effectively cure infantile colic (Çetinkaya and Başbakal 2012). Lavender oil is sedative, anti-colic, and spasmolytic (Buckle 1998). Because of these attributes, it is considered that this oil may be able to ease colic symptoms (England 2008, Buckle 2003). In addition, massage helps relax the smooth muscles of the gut, permitting feces and flatus to pass. This study also discovered that abdominal massage is an excellent therapy for babies suffering from colic (Larsen 1990).

5.9. *Matricaria chamomilla*

Matricaria chamomilla (syn. *Matricaria recutita*) has an essential spasmolytic effect on the intestinal muscle since it has flavonoid constituents (Avallone et al. 2000, Fintelmann 1991). As revealed in human and animal studies, herbs such as *M. recutita* (chamomile) exhibit antispasmodic and antimetabolic properties (Forster, Niklas, and Lutz 1980). Study shows that the topical usage of chamomile oil could be beneficial in treating

colic. Chamomile oil minimized symptoms like crying and fussing in breastfed colicky newborns compared to the infants in the placebo group. 39 and 27 patients in

the chamomile and placebo groups, respectively, reacted to the therapy. There were no detrimental events reported (Sorme et al. 2020).

Table 2: Phytotherapeutic agents with antispasmodic activity.

Scientific name	Phytocompound	Part used	Mode of Action	References
<i>Foeniculum vulgare</i>	Anethole, fenchone	Seeds, fruits	Inhibition of Ca ²⁺ ions by a calcium-antagonist mechanism.	(Iwalewa et al. 2007)
<i>Carum carvi</i>	Carvone, and apiole	Seeds	NA	(Al-Essa et al. 2010)
<i>Mentha piperita</i>	Menthol	Aerial parts	Inhibition of 5-HT ₃ receptor channels, calcium channel antagonism	(Heimes, Hauk, and Verspohl 2011, Grigoleit and Grigoleit 2005)
<i>Zingiber officinale</i>	α -Phellandrene, β -Pinene	Rhizome	Antihistaminergic, antisero-tonergic	(Riyazi et al. 2007)
<i>Zingiber roseum</i>	Limonene, α -Pinene	Seeds	Inhibition of Ca ²⁺ influx.	(Prakash et al. 2006a)
<i>Atropa belladonna</i>	Alkaloids	Roots, leaves	Blocking of muscarinic receptors	(Clissold and Heel 1985)
<i>Fumaria officinalis</i>	Protopine	Flower	NA	(Ivancheva and Tsvetkova 2005)
<i>Melissa officinalis</i>	Citronellal	Aerial parts	Blocking of calcium channels	(Sadraei, Ghannadi, and Malekshahi 2003)
<i>Lavandula angustifolia</i>	Linalool	Leaves, flower	Increase of cAMP	(Lis-Balchin and Hart 1999)
<i>Matricaria chamomilla</i>	Apigenin, bisabolol	Flower	Activation of K ⁺ channels in consort with Ca ²⁺ antagonist effect.	(Avallone et al. 2000)
<i>Anethum sowa</i>	Apiol, l-carvone	Seeds, leaves	Blockade of calcium channel	(Consolini et al. 2011)
<i>Anethum graveolens</i>	d-carvone	Fruit	Ca ²⁺ channels blockage	(Gharib-Nasari and Heidari 2007)
<i>Piper nigrum</i>	Piperine	Fruit	Inhibition of Ca ²⁺ influx	(Nasari and Yahyavi 2008)
<i>Mentha pulegium</i>	Polyphenols	Leaves	Inhibition of Ca ²⁺ influx	(Estrada-Soto et al. 2010)
<i>Perovskia abrotanoides</i>	1,8-cineol, δ -3-carene	Aerial parts	Blockade of calcium channel	(Shah et al. 2013)
<i>Zygophyllum gaetulum</i>	Zygophyloside N	Root	Inhibition of muscarinic receptor and calcium influx	(Aquino et al. 2001)
<i>Eucalyptus camaldulensis</i>	β -Sitosterol	Leaf	Inhibition of synthesis of prostaglandins and cytokines	(Begum et al. 2002)
<i>Lippia thymoides</i>	β -caryophyllene	Leaves	Blockade of Ca ²⁺ influx	(Menezes et al. 2019)
<i>Glycyrrhiza uralensis</i>	Glycycomarin	Roots	Inhibition of acetylcholine and histamine-induced contractions	(Nagai et al. 2006)
<i>Pterodon polygalaeflorus</i>	β -caryophyllene	Seed	Inhibition of Ca ²⁺ entry	(Leonhardt et al. 2010)
<i>Glycyrrhiza glabra</i>	Isoliquiritigenin	Roots	Blockade of the calcium channels	(Chen et al. 2009)

5.10. *Anethum sowa*

Anethum sowa (Indian Dill) has been utilized in various countries and communities since ancient times. Particularly, seeds, leaves, and whole plant of *A. sowa* are used for the cure of various diseases. Anethi oil, extracted from *A. sowa*, is used as a flavoring, carminative, and spasmolytic agent. In India, *A. sowa* gripe water is administered to diminish colic pain and treat flatulence and indigestion in infants, young kids, and expecting women (Pulliah 2002). The essential oil in the seed of *A. sowa* eases intestinal spasms and griping that aids in curing colic (Duke 2002).

5.11. *Anethum graveolens*

The most well-known ethnobotanical applications of *A. graveolens* (Dill) are antispasmodic and anti-hiccup effects in newborns. It possesses anticonvulsant, antiemetic, and muscle relaxant properties. Complementary to these folkloric applications, *A. graveolens* also helps with flatulence, stomach discomfort, and indigestion. It soothes pain and has a relaxing effect on dysmenorrhea (Heidarifar et al. 2014). Dill contains rutin, flavonoids, quercetin, and their derivatives, as recognized by phytochemical studies (Gebhardt et al. 2005, Möhle, Heller, and Wellmann 1985). The spasmolytic effect of dill extract on isolated rat ileum is instigated by the quercetin and rutin components (Cimanga et al. 2010).

5.12. *Piper nigrum*

Piper nigrum (black pepper) is very popular in traditional medicine across many countries. The scientific world has extensively explored the biochemical nature of this plant, and a plethora of literature has been gathered. *P. nigrum* fruit extract was studied to analyze its antispasmodic activity on rat ileum. The antispasmodic activity of the black pepper extract on rat ileum was possibly arbitrated by inhibition of Ca²⁺ influx (Naseri and Yahyavi 2008).

5.13. *Mentha pulegium*

M. pulegium is a tiny plant with dark green or grey leaves. Locally, it is referred to as squaw mint or pudding grass. It is traditionally employed in Mexico to treat GIT diseases. The different solvent extracts of *M. pulegium* have been studied for their spasmolytic action on isolated rat ileum. Because of its antagonistic impact on calcium channels, *M. pulegium* showed a substantial

relaxing effect on isolated intestinal tissues of rats (Estrada-Soto et al. 2010).

5.14. *Combined Herbal Therapy*

Herbal tea formula comprising *V. officinalis*, *G. glabra*, *M. chamomilla*, *M. officinalis*, and *F. vulgare* was effective in eradicating colic in comparison with a placebo tea preparation (Weizman et al. 1993). An herbal mixture (ColiMil) combining *M. chamomilla*, *F. vulgare*, and *M. officinalis* could be useful for the management of IC in breastfed and bottle-fed babies. ColiMil dramatically lowered crying time in babies when compared with a placebo. The study found that infants experienced sleepiness, constipation, and nausea. Nevertheless, none of these side effects were detrimental, and there was no distinction observed in the event of side effects between the herbal formula preparation and the placebo (Savino, Cresi, et al. 2005)

5.15. *Digas Colic Drops*:

Digas colic drops (DCD-684) were investigated for spasmolytic effects using five different medicinal herbs, i.e., *Z. officinale*, *M. piperita*, *F. vulgare*, *M. arvensis*, and *C. carvi*. DCD-684 was shown to have antispasmodic effects on both KCl-induced and spontaneous contractions. The addition of ample phytochemicals in DCD-684 led to synergistic effects. (Roome et al. 2021).

6. Expert Opinion

Conclusively, numerous interventions such as behavioral therapy, dietary modifications, pharmacological interventions, and manipulative techniques are available for treating colic. However, synthetic drugs such as dicyclomine, simethicone, and cimetropium that are accessible for treating colic have adverse effects, low efficacy, and are expensive to manufacture. Moreover, probiotics could be useful for treating colic, but long-term evidence is lacking. Numerous plants with antispasmodic activity have been employed as a natural, economical alternative with no or low side effects to treat colic symptoms. Various traditionally used medicinal plants are rich in chemical ingredients that have proven to be novel drug candidates. These chemical ingredients can be applied to treat several GIT disorders. Although minimal evidence is available for medicinal plants, they are neither detrimental nor costly. It is suggested that more research be conducted on medicinal plants to assess their efficacy and safety for treating colic. Clinical trials should be carried out to

validate the efficacy and divulge the safety profile of phytochemicals to treat spasmodic disorders. It may also be desirable to test multiple doses of phytochemicals to better understand their alleged dose-dependent impact.

Conflict of Interest

The authors declare that they have no competing interests.

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Study Approval

NA

Consent Forms

NA.

Authors Contribution

HI conceptualized the study and wrote the final manuscript, AH helped in the analysis and writing the first draft, did the review analysis, and SJ supervised the whole project and wrote the final manuscript.

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