Peppermint

Mentha piperita

AN OVERVIEW OF ITS BIOLOGICAL ACTIVITIES AND MECHANISM OF ACTIONS

Scientific report
authored by

groupe berkem

Peppermint *(Mentha piperita)*, is an **aromatic plant**, from the Lamiaceae family that grows throughout temperate regions of Europe, Asia, United States, India and Mediterranean countries. Peppermint is a crossed-hybrid mint of watermint (*M. aquatica L.*) and spearmint (*M. spicata L.*). Fresh and dried plant materials are used in **food industry** as flavoring agents but also in **cosmetics**. It is widely used to make tisanes.

Mint plants have a **long history of medicinal use**, dating to ancient Egypt, Greece, and Rome where they were used as **stomach soothers and traditionally used to helps symptomatic relief of digestive disorders and as an aid for the digestion** [1].

Physiology and management of Gastrointestinal disorders

Functional gastrointestinal disorders (GID) are variable **combinations of chronic or recurrent gastrointestinal symptoms** not explained by structural abnormalities [2]. They affect **millions of people of all ages** – men, women, and children. They are the most commonly presented GI illnesses seen by doctors in primary care or gastroenterology [2].

GID encompass a variety of troubles in which the **motility** (low, high motility or spasms) or **sensitivity** of the GI tract are altered. Problems occur when nerves or muscles in any portion of the digestive tract do **not function in a coordinated fashion**, or when the sensitivity of the nerves of the intestines or the way in which the brain controls some of these functions are impaired. Most frequently, the GID appears when the **enteric nervous system, also called our "second brain" is altered**. Indeed, the gastrointestinal (GI) tract is innervated by an extensive intrinsic network of ganglion-rich nerve connections known as the enteric nervous system (ENS) [3]. The human ENS contains approximately **400-600 million neurons** [4].

The primary role of the enteric nervous system is to ensure **proper digestion**. It oversees intestinal motility - also known as peristalsis - the rhythmic contractions of the digestive tract that move food and liquids through it. Additionally, it regulates the **secretion of digestive substances** like enzymes and hormones and plays a key role in **nutrient absorption** [5]. Capable of sensing, interpreting, and responding to various signals from the gut, it can detect irritants, toxins, or pathogens and initiate an appropriate response, such as increasing the production of protective mucus [5, 6]. Despite its autonomy, the enteric nervous system does not operate in isolation. It **interacts closely with numerous biological systems** including the immune system and the gut microbiota [6, 7]. Moreover, it maintains

constant communication with the central nervous system, via the vagus nerve [8]. Generally, these interactions foster the smooth functioning of our body.

However, when the equilibrium is broken, gastrointestinal disturbances like gut discomfort or spasms can emerge. Gastrointestinal spasms are sudden, involuntary contractions of the smooth muscles in the GI tract. These spasms can be painful and disruptive, and they are associated with various gastrointestinal disorders. The underlying physiological pathways that contribute to GI spasms involve **neural signaling, neurotransmitter releases, inflammatory responses, and ion channel regulation**. Some those key mechanisms are depicted in the next paragraph.

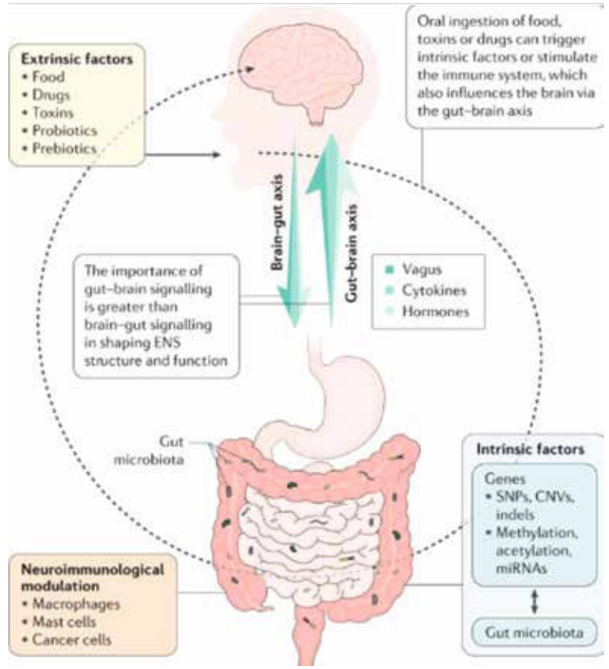


Figure 1: Modulation of the gut-brain-axis and the enteric nervous system (Niesler et al., 2021).

Serotonin (5-HT), plays a major role in communication between the brain and the gut as 90% of serotonin is produced in the gut enterochromaffin cells from dietary tryptophan. Serotonin produced in the gut regulates peristalsis and motility through serotonin receptors (5-HT receptors), where 5-HT3 and 5-HT4 subtypes are the most [9]. Overactivation of serotonin receptors can lead to an increase in motility and thus diarrhea, by activation of 5-HT3 receptors [10, 11]. Overactivation can also lead to stimulation of peristalsis and fluid secretion via 5-HT4 receptors. In some conditions, there may be also abnormalities in serotonin release and uptake, leading to hypersensitivity and altered motility[10, 11]. Spasmolytic agents targeting these pathways can modulate gut movement, either reducing excessive contractions or promoting relaxation [10-12].

Voltage-gated calcium channels are known to regulate smooth muscle contractions in the GI tract by the influx of calcium ions. These channels are involved in neuronal activation and pain perception. When spasmolytic activity is altered, these channels are either overstimulated or under-inhibited, leading to either excessive contraction (spasms) or reduced motility (hypomotility). For example, blocking voltage-gated potassium and sodium channels has been shown to reduce pain sensitivity [12, 13].

Inflammatory mediators, such as cytokines, histamines, prostaglandins released from immune cells (e.g., mast cells) and neuropeptides, play a role in spasmolytic regulation and contribute to peripheral sensitization of mucosal neurons, leading to visceral hypersensitivity. Increased inflammation can lead to enhanced contractility and pain by sensitizing the smooth muscle and nerve endings. Therefore, in conditions of altered spasmolytic activity, controlling inflammation is crucial to reducing GI tract hyperactivity [6, 9, 12].

Acetylcholine, released from the parasympathetic nervous system, binds to muscarinic receptors on smooth muscle cells, stimulating contractions. Spasmolytic drugs like anticholinergics block these receptors, reducing excessive contractions and relieving spasms. However, if this pathway is overly inhibited, it can result in constipation and sluggish GI motility [14].

Transient Receptor Potential Vanilloid Type I (TRPV1) and Ankyrin 1 (TRPA1). TRPVA1 and TRPA1 are both members of the Transient Receptor Potential (TRP) family of ion channels. In the gastrointestinal (GI) system, TRPA1 and TRPV1 are involved in sensory nerve signaling, gut motility, and visceral pain perception. For example, during gut inflammation, pro-inflammatory molecules can lower the activation threshold of both receptors, making the gut more sensitive to normal stimuli. Their activation can also lead to increased peristalsis or even spasms in conditions where the gut is irritated or inflamed [12, 15, 16].

Biological properties of peppermint.

As reported in several monographies, peppermint has been used traditionally **to relieve a panel of symptoms associated with digestive disorders such as dyspepsia, flatulence and an aid for digestion** [1]. The scientific literature confirmed those traditional uses and effects.

In preclinical studies, the **antispasmodic effect** of peppermint has been demonstrated with different extraction types. An alcoholic extract of peppermint leaf on animal samples of ileum was evaluated and compared to other plant extracts notably, *Rosmarinus officinalis*, *Carum carvi*, *Melissa officinalis*, etc. The peppermint extract tested, demonstrated antispasmodic effects on the isolated guinea pig ileum at 2.5 and 10.0 ml/L (1:3.5, ethanol 31% w/w) [18]. A dose response relaxing effect on gastrointestinal smooth muscles was also described with an aqueous extract of peppermint on the rat ileum [19]. Moreover, another aqueous extract of peppermint exhibited dose-dependent relaxation effects on isolated rabbit duodenum, with dried leaf extracts being more effective than fresh ones [20]. As depicted in previous study, the effect of peppermint extract was more effective than the other plants tested in the same model (fennel, dill and cumin).
Those results confirmed that aqueous and ethanolic extracts of peppermint have relaxation effects on different parts of the GID, notably the ileum and duodenum.

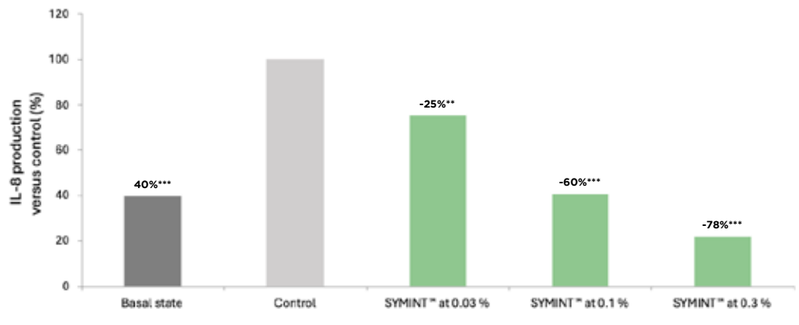
One feature of peppermint leaves is its content in **essential oil**, obtained by steam distillation of the fresh leaves. Several studies reported its ability to act as an anti-spasmodic and analgesic effects both in preclinical and clinical studies.

In several preclinical models the used of **Peppermint oil** (PMO) or its main constituent **menthol** demonstrated that they are able to **induce the relaxation of ileal smooth muscle** [21], **decrease the contractile responses** in the guinea pig tenia coli [22], the **contractility of small bowel and duodenal contractions** [23]. PMO can **reduce visceral pain** in animal models when combined with caraway oil [24]. Based on those results, several clinical studies tested the efficacy of peppermint oil in intestinal bowel syndrome. Meta-analysis concluded of the **superiority of peppermint oil vs. placebo to alleviate symptoms of IBS**. Nevertheless, they pinpointed that adverse events (heartburn, gastro-oesophageal reflux, dyspepsia, or flatulence) were more frequent in the PMO group compared to the placebo [25, 26].

Mechanism of actions.

The **anti-inflammatory** effect of peppermint extract has been demonstrated in the literature [27].

SYMINT™ was evaluated internally at Group Berkem in an intestinal cell line (HT-29) by the quantification of IL-8 production in response or not to a pro-inflammatory agent: lipopolysaccharide (LPS) from *Pseudomonas aeruginosa*. SYMINT™ tested, decreased IL-8 production in a dose dependent manner in non-inflammatory or inflammatory cell environment. Compared to control, the highest dose of SYMINT™ induced a decrease of 78% of IL-8 production.



**p<0.001; ANOVA followed by Dunnett's post-hoc test

Figure 2: Effect of SYMINT™/ mint extract on IL-8 production after an LPS challenge in HT-29 cell line.

These results confirm that the characteristics of our extract possesses *in vitro* anti-inflammatory effects as already demonstrated for others type of extracts in the literature (for review see [27]).

In the literature, the **antispasmodic effect** of peppermint extracts were mainly tested after electrical stimulation with or without different chemical agents. The preclinical evaluation of the antispasmodic effect of peppermint extract was tested in guinea pig ileum with acetylcholine or histamine as spasmogenic agents. The peppermint extract tested shifted the dose response curves of acetylcholine and histamine to the right in a dose dependent manner and a significant decrease of the maximal possible contractility was observed. In histamine-induced contractions decreased the maximal possible contractility produced by histamine [18]. As the previous study, the antispasmodic activity of the peppermint was also show by another animal study. The peppermint aqueous extract elicited a rightward shift in the dose-response curve of potassium chloride (KCl) without altering the maximum response. These findings suggest that the extract antagonizes acetylcholine (Ach)- and KCl-induced contractility in rat ileal smooth muscle. Moreover, the data indicate that the inhibitory effect of the peppermint extract on Ach-induced contractility is likely non-competitive. The observed reduction in KCl-induced contractility further implies that the peppermint extract may exert its effects, at least in part, through modulation of calcium channels in ileal smooth muscle [19]. The spasmolytic activity of an infusion of peppermint was tested on the longitudinal coat of smooth muscle of the ileum of guinea pigs. In this study, after electrical stimulation of the segments, different substances (acetylcholine, atropine, norepinephrine, prazosine, yohimbine, and phenylephrine) were applied to identify the mechanism of action of peppermint. When the test solution of the peppermint extract is added after the addition of phenylephrine a reduction of muscle contraction was observed, meaning that the anti-spasmodic effect of peppermint may be attributed to a a1 blockage [28].

PMO shares identical mechanism of actions with peppermint extract but some are specific to the essential oil. For example, the smooth muscle relaxant effect of the PMO, mainly due to the presence of menthol is mediated via calcium channel-blocking properties in guinea pig ileal smooth muscle (3,12]. PMO was also able to attenuate contractile response in guinea pig taeni coli in response to acetylcholine, histamine, tryptophane and substance P (3, 13). Those results were attributed to the fact that PMO is able to decrease the influx of extracellular calcium ions through voltage-dependant channels and transient receptor potential melastin 8 (TRPM8) channels on gastrointestinal smooth muscle [29]. Moreover, in mouse small intestine, menthol may affect the enteric nerve system directly via the interstitial cells of Cajal (ICC), the pacemaker cells of the GI tract. Emerging evidence suggests also that menthol's analgesic effects on visceral pain are mediated via TRPA1 receptors [30, 31].

Conclusion

Functional GID involve a finely-tuned **balance of neural, hormonal, and inflammatory pathways** that regulate smooth **muscle contraction, motility, and sensitivity**. Several mechanisms are implied such as cholinergic, serotonin, and inflammatory pathways. Peppermint extracts aim to **restore this balance by modulating these pathways**, reducing abnormal spasms, and alleviating symptoms in GI disorders.

Why Groupe Berkem?

- ✓ Pioneer in plant extraction for over 60 years
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Contact us
groupeberkem@berkem.com

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