*Technical Report*

# Significance of Betaine HCl in CanXida Remove (Formula RMV)

*Betaine HCl in CanXida Remove (Formula RMV) restores pH levels of the digestive system to discourage bacterial and fungal colonization in the stomach and the small intestine. It also helps resident probiotic microbial flora to grow, by providing suitable conditions for growth and proliferation.*

## Contents

## Executive Summary

Betaine HCl is categorized as a dietary supplement and over-the-counter food product under Article 21 of the FDA Code of Federal Regulations (CFR). It has been proven effective in restoring stomach pH and regulating the acidic conditions of the digestive system for food digestion, growth of acidophilic probiotic bacteria, and eliminating bacterial overgrowth in the stomach and small intestine. It is also effective against opportunistic fungal pathogens such as *Candia albicans* which enjoy mildly acidic conditions for colonization when stomach acid is not sufficient to maintain the lower pH levels*.

Betaine HCl in CanXida Remove (Formula RMV) provides support to antimicrobial ingredients of the formulation for the removal of candida colonies from the stomach and small intestine as well as to counter SIBO and bacterial pathogens. It also maintains the stomach gastric barrier to discourage bacterial and fungal growth of pathogens and opportunistic microbes. The extended-release formula of CanXida Remove (Formula RMV) adds to its efficacy and effectiveness as it can act for a prolonged period of time by maintaining low pH levels in the stomach and duodenum*.

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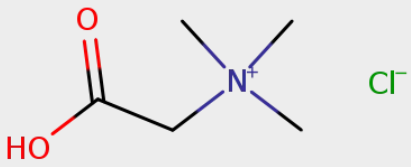
## 1. Introduction

Betaine hydrochloride, also known as betaine HCl, is a derivative of betaine (also called betaine anhydrous). Although betaine and betaine HCl are slightly different in chemical composition, they have distinctly different physiological roles in the body. Betaine is naturally present in various foods including vegetables, grains, and seafood, and is rarely deficient in the body. On the other hand, betaine HCl is neither present in the foods nor synthesized within the human body. Betaine acts as a raw material for the metabolism of amino acids within the body. On the contrary, betaine HCl is used to regulate gastrointestinal secretions and acidic pH to maintain its physiological activity in the stomach and small intestine.

Candida albicans is a commensal yeast living in the gastrointestinal tract where it normally participates in probiotic activities including maintaining microbial balance and nutrient absorption, except in the stomach and duodenum (the first part of the small intestine

**Caprylic Acid**

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|---|---|
| Generic Name: | Betain Hydrogen Chloride |
| Drug Bank Accession Number: | DBSALT001448 |
| Drug Bank Status: | Approved, |
| Drug Category: | Small Molecule, Nutraceutical |
| FDA UNII: | JK8U8K4D6K |
| WHO Approval Date: | Aug. 17, 1988 |
| Updated: | Jun. 7, 2023 |
| CFR CITE: | 21CFR310.540 |
| FDA Classification: | OTC (Over the Counter) Dietary Supplement |
| Other Names: | Betaine HCl |
| Chemical Formula: | $C_5H_{12}NO_2.Cl$ |
| Molecular Weight: | 153.61 g/mol |

attached to the stomach). The acidophilic (acid-loving) probiotic bacteria dominate the stomach and duodenum. Hydrochloric acid produced by the stomach under normal physiological conditions keeps in check any fungal outgrowth in these regions. However, low acid production in the stomach (due to medical, health, food, or physiological issues), does not provide enough protection against yeast outgrowth in the stomach and duodenum, ultimately leading to bacterial and fungal outgrowths. Small intestine bacterial outgrowth (SIBO) is a typical condition caused by low stomach HCl levels that encourage non-acidophilic bacteria and fungi to penetrate the stomach and duodenum (Giamarellos-Bourboulis et al 2016).

Furthermore, stomach HCl is also crucial for protein denaturation and breakdown before it enters the intestine. Intact proteins entering the intestine trigger immune cells such as resident macrophages and dendritic cells, leading to IBD (inflammatory bowel diseases). The intestine hosts a large colony of resident immune cells, and it is necessary to neutralize any immune triggers in the stomach by HCl (Steinbach et al 2014).

Betaine HCl is a dietary supplement with the intended use of stomach acidification rather than a nutrient. FDA-recommended use for betaine HCl is also a stomach acidifier. Yago and colleagues from the Department of Bioengineering and Therapeutic Sciences, University of California, San Francisco reported that betaine HCl restores the pH of the stomach (Yago et al 2013). Restoration of stomach pH is critical for maintaining a balanced probiotic flora in the stomach and duodenum and to ward off proliferating and intrusive pathogenic bacteria and candida yeast.

## 2. Health Benefits of Betaine HCl

It is a well-known fact that malnutrition causes health problems due to insufficient nutrient supply. However, even when the nutrient supply is adequate, poor digestion and malabsorption due to insufficient gastrointestinal activity can lead to fatigue, exhaustion, and related symptoms of malnutrition. Betaine HCl restores not only normal gastric activity but also provides antimicrobial assistance and helps regulate bowel movements.

### 2.1. Restoring stomach pH

The main purpose of betaine HCl is to replenish stomach pH (Guilliams et al 2020). Normally, HCl produced by the stomach wall is enough to denature proteins, kill microbes that tag along with food, and help digest food by activating pepsinogen. Unhealthy nutrition practices or physiological stresses can cause stomach walls to become thin and swollen which results in less gastric secretions and stomach pH is raised above 4. Stomach acid maintains a pH of around 2 for proper antimicrobial activity and to ensure protein digestion. A pH of 4 or above invites hostile microbes such as bacteria and fungi to colonize the small intestine and stomach which can spread to the esophagus and mouth. Betaine HCl replenishes the stomach acid to avoid the above-mentioned complications.

> ***Indications of low stomach pH are the same as those of acidity, i.e., heat burn, chest pain, etc., and taking antacids often aggravates the condition.***

Medicines that lower stomach pH and inhibit HCl production in the stomach are commonly prescribed. These include proton pump inhibitors (antacids) and antihistamines (anti-allergy) medicines. These medicines are usually prescribed for longer duration which allows pathogenic and opportunistic microbes to colonize the stomach. These pathologies persist even after medicine intake is stopped, leading to a disturbed microbiome of the gastrointestinal tract with far-reaching implications. Betaine HCl is often recommended to restore the stomach's acidic conditions and to discourage any pathogenic microbial overgrowth. Figure 1 demonstrates the effect of Betaine HCl on restoring stomach pH*. Dr. Guilliams from the School of Pharmacy, University of Wisconsin, US demonstrated that mealtime supplementation of betaine HCl to patients suffering from low stomach HCl was significantly associated with improved digestive function (Guilliams & Drake 2020).

Stomach pH is also essential for mineral absorption such as iron and calcium which play essential metabolic functions. Vitamin B12 also needs acidic conditions in the stomach for absorption in the intestine. Betaine HCl ensures that these micronutrients are properly absorbed when the stomach is not physiologically fit. Maintenance of the acidic pH of the stomach is essential for downstream digestion and absorption of food in the small intestine and large intestine as well.

### 2.2. The "Gastric Barrier"

Gastric juice (a combination of HCl and pepsinogen) is not simply for food digestion, but it provides an important line of defense. Betaine HCl helps in maintaining this barrier

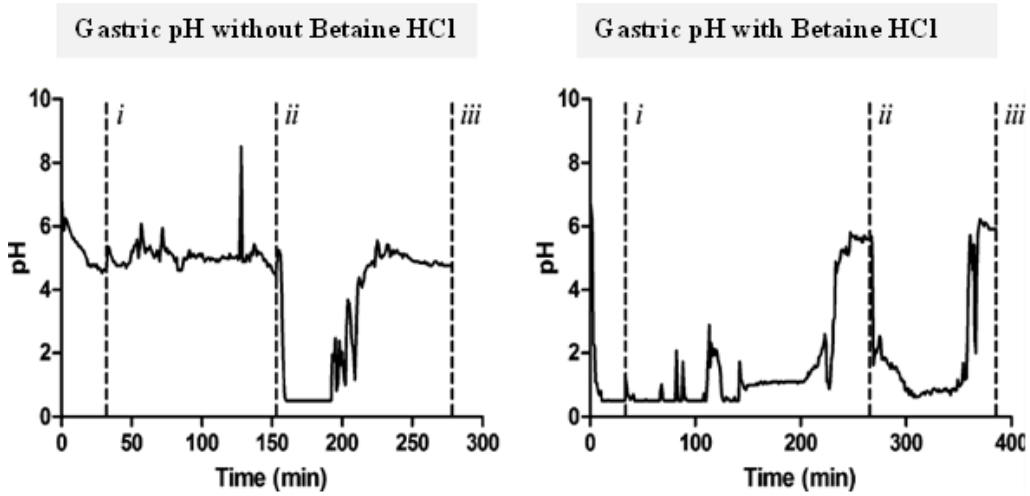


***Figure 1:*** *Effect of Betaine HCl supplementation on restoring pH of the stomach on two healthy volunteers. Stomach pH without Betaine HCl supplementation (on the left) remained considerably higher than usual compared to the individual taking Betaine HCl (on the right). Graph borrowed from American Chemical Society, published by Yago and colleagues (Yago et al 2013)*

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when gastric acid pH is not up to par (Martinsen et al 2005).

Besides activating enzymes, HCl is essential for denaturing proteins and killing microbes coming along with the food. Protein denaturation inactivates antigenic moieties of proteins by breaking the peptide bonds. Otherwise, the immune system triggered by food proteins will recognize food as an antigen leading to inflammation of the gastrointestinal wall to avoid absorption. It typically happens during food allergies, but lower HCl levels can trigger the same symptoms.

HCl is also necessary to kill food-borne pathogens such as *Entamoeba, Cholera, Shigella, and Salmonella*. Low production of HCl in the stomach gives these pathogens a free pass to the intestine leading to serious health problems (Howden & Hunt 1987; Hurst 1934). HCl neutralizes pathogens coming with food. Betine HCl provides the necessary conditions for the stomach to carry out its normal physiological functions of protein denaturation and antimicrobial activity.

### 2.3. Restoring Microbial Balance

Probiotic bacteria thriving in the acidic pH of the stomach and duodenum cannot survive in higher pH levels. Higher pH levels encourage opportunistic bacteria and fungi to colonize the stomach and duodenum. These opportunistic microbes transform into pathogenic strains, producing inflammation and weakening the mucosal layer.

Betaine HCl lowers the stomach pH levels by providing protons (hydrogen ions). The lower pH not only encourages the colonization of good bacteria but also acts as a natural antimicrobial for opportunistic and pathogenic strains of fungus and bacteria. The same is true for *Candida albicans* which normally reside in higher pH areas in the gastrointestinal tract as it cannot survive acidic conditions. However, when stomach HCl levels are low and its pH rises above the normal physiological levels, nutrient-rich

***Table 1**: Probiotic bacteria that need acidic pH to survive in the stomach. Betaine HCl is crucial to maintaining an acidic pH.*

| Probiotic Bacteria from Food Sources |
|---|
| Lactobacillus delbrueckii subsp. bulgaricus |
| Ligilactobacillus acidipiscis |
| Lactobacillus acidophilus |
| Lactobacillus delbrueckii subsp. lactis |
| Levilactobacillus brevis |
| Lacticaseibacillus casei |
| Lactiplantibacillus plantarum |
| Loigolactobacillus coryniformis subsp. coryniformis |
| Lactobacillus helveticus |
| Levilactobacillus parabrevis |
| Lacticaseibacillus paracasei subsp. paracasei |
| Lactiplantibacillus pentosus |
| Lactiplantibacillus plantarum subsp. plantarum |
| Weissella hellenica |
| Weisella paramesenteroides |
| Weisella confusa |

areas of the stomach and duodenum become easier to colonize.

Betaine HCl is also essential to ensure that acidophilic probiotic bacteria coming with food can thrive in the stomach. Table 1 shows the probiotic bacteria that need acidic pH to survive in the stomach and the small intestine. The gastrointestinal tract constantly needs to be replenished with probiotics from food sources, which is not possible under pH fluctuations as different regions of the gastrointestinal tract host different groups of probiotic flora depending on the pH levels.

### 2.4. Small Intestine Bacterial Overgrowth (SIBO)

The human gut hosts a diverse community of microorganisms that interact with each other as well as with the human immune system and gut cells producing a self-balancing microbiome. These microbes are densely populated in the large intestine, but small numbers are also found in small intestinal regions such as the duodenum and jejunum. The food coming from the stomach to the intestine is significantly acidic to discourage any bacterial growth. Moreover, the duodenum also receives plenty of bile from the gall bladder and pancreatic juice from the pancreas. These secretions, along with HCl, function as strong antimicrobials and only selective probiotic bacteria can survive under these conditions.

However, this balance is disturbed when digestive secretions are insufficient (regardless of the reason). In that case, it leads to the growth of bacteria in the small intestine called Small Intestinal Bacterial Overgrowth (SIBO). SIBO symptoms include bloating, excess gas, abdominal discomfort, diarrhea, poor digestion, and weight loss (Quigley et al 2020).

A low level of stomach HCl is a clinical risk factor for SIBO (Bures et al 2010; Lewis et al 1996). One of the ways to control bacterial overgrowth and restore the normal microbial flora in the small intestine is to restore the acidic pH of the stomach using dietary supplements like betaine HCl. It provides necessary acidic conditions suitable for resident microbial flora and discourages the growth of opportunistic bacteria and fungi.

Under low gastric secretions, the bacteria from the oral cavity get a free pass to the small intestine and bacteria from the large intestine also creep up as time passes. SIBO is characterized by an imbalance of bacterial diversity which resembles more like colonic and oral probiotic bacteria containing *Streptococci* (71%), *Escherichia coli* (69%), *Staphylococci* (25%), *Micrococci* (22%), and *Klebsiella* (20%). These bacteria break down bile acids, hence the body cannot digest fats and cannot absorb essential fatty acids in adequate amounts (Quigley & Quera 2006). These bacteria also release enterotoxins and enzymes that damage the cells along the intestinal wall causing long-term damage, changing villi patterns, and affecting nutrient absorption, especially vitamin B12.

It has been well established that betaine HCl restores stomach pH and is clinically proven (clinical trial ID: NCT01237353). Betaine HCl restores the “gastric barrier” to kill bacteria coming with food or from the oral cavity. Betaine HCl also prevents colonization of the small intestine with bacteria from the large intestine and colon *.

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## 2.5. Candida Infection

*Candida albicans* is a commensal microorganism normally residing in the oral cavity and large intestine. It does not do any harm when gut microbiome is well-balanced. However, it turns pathogenic when conditions are favorable to do so (opportunistic pathogen). Candida yeast cannot grow and reproduce under acidic conditions of the stomach and small intestine at pH 2.0 and below. However, it grows best under mildly acidic conditions at pH 4.0 – 6.0 which are normally present in the mouth and large intestine. When gastric juice production in the stomach is diminished, the pH of the stomach becomes less acidic and candida yeast coming with food from the mouth can thrive in the stomach. As conditions in the stomach are different as compared to the oral cavity, it overgrows which extends to the small intestine leading to small intestine fungal overgrowth (SIFO).

Dr. Daniell (MD) from the Department of Family Practice, the University of California Medical School at Davis, Davis, California, USA published a report stating that candida starts to grow in the low acidic conditions of the stomach in patients taking antacids (proton pump inhibitors). Antacids lower HCl production and disrupt gastric barrier (Daniell, 2016). Similarly, Jacobs and colleagues from the Department of Internal Medicine, the University of Iowa Carver College of Medicine, Iowa City, IA, USA, reported that 63% of patients suffering from SIBO also develop SIFO and candida infection when stomach pH is higher than the usual (Jacobs et al 2013). These results are in support of similar studies suggesting lower HCl production in the stomach invites candida colonization (Gościmski et al 2002; Karmeli et al 1995).

As *Candida albicans* grow best in mildly acidic conditions as shown in Figure 2, it is essential to regulate stomach pH while treating the overgrowth of bacteria and fungi in the stomach and small intestine. Betaine HCl restores stomach pH to normal physiological levels when the stomach is not producing enough HCl due to infection load, physiological stresses, or medical conditions.

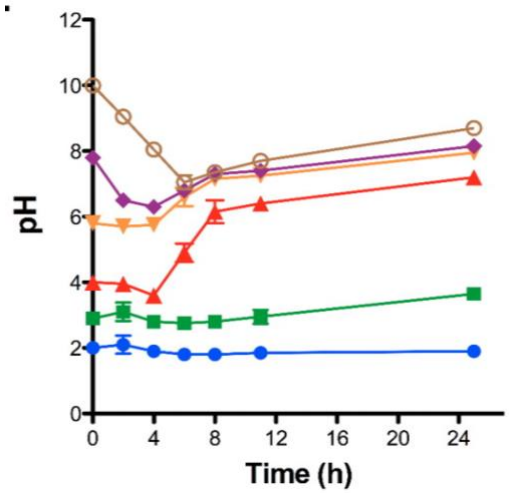


***Figure 2**: The effect of pH on the candida growth. At lower pH levels (2.0 – 3.0, as shown in blue and green lines, candida does not grow over time. However, its growth becomes rapid when pH is raised to 4 or above (red and orange lines). Graph borrowed from American Society of Microbiology, published by* Vylkova and colleagues (Vylkova et al 2011).

Betaine HCl as a dietary supplement can be helpful not only for controlling SIBO and food digestion but also for controlling candida infection and fungal overgrowth in the small intestine.

## 3. Biosafety profile

Betaine hydrochloride is categorized as an over-the-counter dietary supplement by the FDA and WHO. In clinical trials on healthy human volunteers, it regulates the stomach pH without any side effects (Yago et al 2013). Betaine and hydrochloric acid are produced within human cells and are part of normal metabolism as well.

Betaine hydrochloride dissociates in the stomach to release proton (hydrogen ions) leaving behind the betaine moiety. It can be readily absorbed in the small intestine and is completely metabolized in the liver and kidneys. Betaine hydrochloride is generally safe to administer through the oral route in quantities found in food and dietary products. It is also classified as an over-the-counter drug by the Code of Federal Regulation (CFR) under Article 21.

Clinical research studies on human volunteers have demonstrated the efficacy of betaine hydrochloride in regulating the stomach pH without any side effects (clinical trial IDs: NCT02758015; NCT01237353; NCT01398046). Betaine hydrochloride has been approved since 1988 as a dietary supplement and its status remained unchanged during a recent review by FDA and WHO in June 2023.

## 4. Significance of Betaine HCl in CanXida Remove

CanXida Remove (Formula RMV) is a dietary supplement designed to counter the full spectrum of microbial infections in the digestive system. It contains natural extractives and bioactive compounds from different plant-based sources with antifungal, antibacterial, and antiprotozoal properties. However, the efficacy of antimicrobial ingredients in CanXida Remove will not attain full potential if the digestive system does not provide a suitable environment for the bioactive compounds to combat microbial overgrowth and infections. Betaine HCl not only provides suitable pH for absorption and activity of antimicrobial ingredients, but also restores the physiological state of the stomach and small intestine for an effective approach to eliminating pathogens.

CanXida Remove (Formula RMV) is a controlled-release dietary supplement, that releases its ingredients over an extended period of time. It is especially significant for betaine HCl activity to maintain the pH of the stomach for extended periods and to eliminate any candida colonies. As candida and SIBO are pH-dependent conditions arising from low HCl productions in the stomach, CanXida Remove formulation with extended and sustained release of betaine HCl effectively removes fungal and bacterial colonies in the stomach and small intestine by restoring the acidity*.

In conclusion, betaine HCl restores physiological conditions of the digestive system, especially in the stomach and small intestine. It restores pH, maintains the gastric barrier, and prevents candida colonization in the stomach and duodenum. It also encourages the growth of acidophilic probiotic bacteria to maintain the probiotic balance of the microbiome. Betaine HCl is also essential for the activity of other ingredients in the CanXida Remove (Formula RMV) as well as for proper food digestion when stomach is under microbial stress.

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