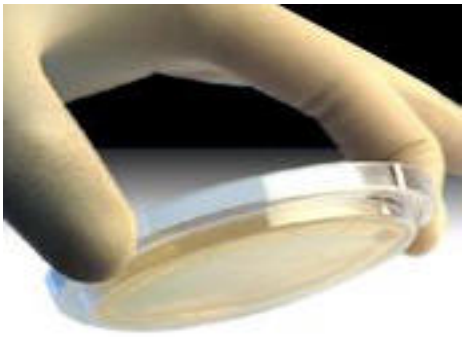
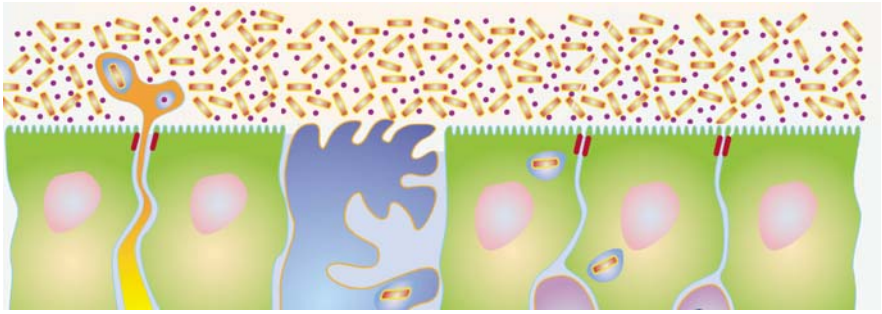
Pathogen inhibition





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Content

Introduction

The human gastrointestinal tract is populated with as many as 100 trillion bacterial cells. This means over 90% of the total amount of human body cells are bacteria cells, the so called intestinal microbiota. At this point, over 2000 species are identified as being part of the human microbiota. The identification of new species is still ongoing and as new identification techniques arise, this number will probably continue to rise.

The intestinal microbiota acts at three different levels inside the intestine (figure 1)[1].

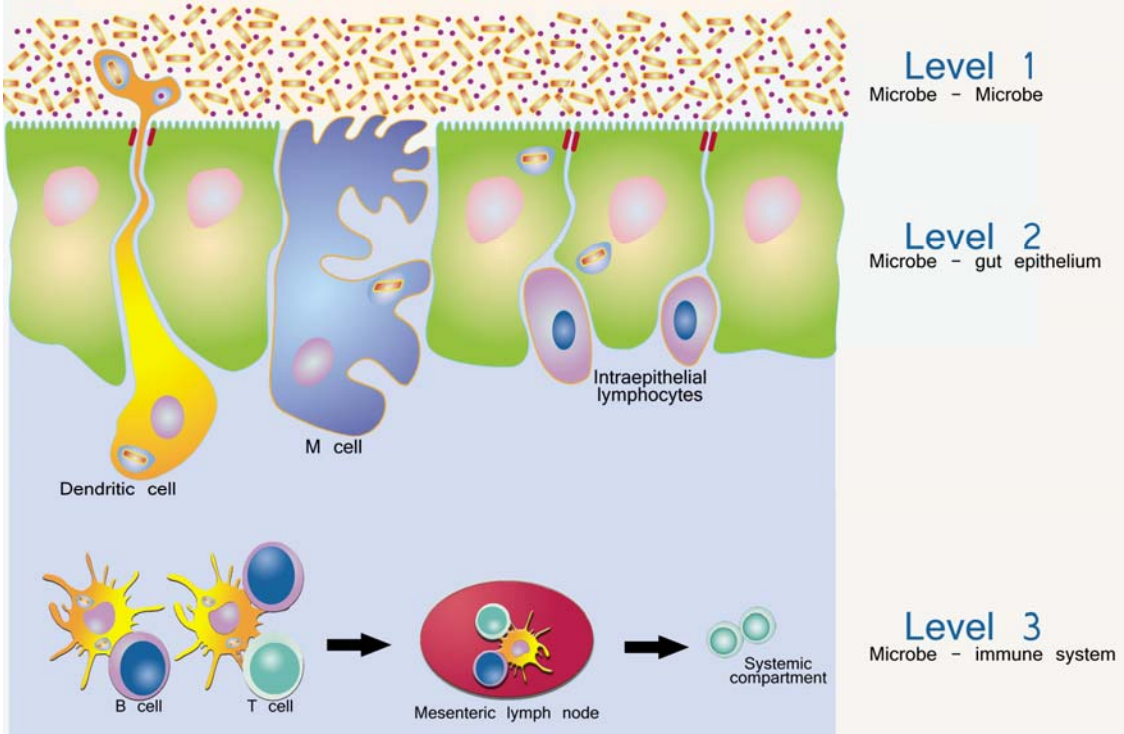


Figure 1: the different levels of action of a healthy the microbiota and probiotics. Level one includes microbe-microbe interactions, level two where the microbes interact with gut epithelium cells and level three, the interaction of the microbiota with the immune system.

Level one describes the microbe-microbe interactions. Bacteria compete for nutrition, adhesion sites and produce metabolites and antimicrobial substances against pathogenic species. A healthy gut microbiota prevents the colonisation of pathogenic bacteria in the gut.

At level two, bacteria inside the intestine are able to strengthen the barrier function of the gut barrier via several pathways. Mechanisms include the increase in mucus production, the strengthening of the tight junctions and the regeneration of epithelial cells.

At level three, the microbiota can stimulate the immune system to produce cytokines and antibodies against pathogenic bacteria, for example the antibody Immunoglobulin A (IgA), which is able to attack pathogens.

Due to different stress factors such as an unbalanced diet, the use of antibiotics, endurance sports, travelling or physiological stress, the balance in the intestinal microbiota can be disturbed. Probiotics are designed to prevent or treat disturbances in the intestinal microbiota. It is shown that multispecies probiotics are more effective than monostrain probiotics, since these multispecies can be active at all three levels [1]. This report focuses on pathogen inhibition, so on level one. Probiotics can produce bacteriocins and lactic acid and thereby inhibit the growth of pathogens.

Due to a stress factor and the hereby caused disturbance of the microbiota, an overgrowth of pathogens is possible. Depending on the pathogen, the overgrowth can cause long or short term disturbances in the gut and can lead to several disorders. One of the most researched examples is the overgrowth of ETEC, which is associated with the development of travellers' diarrhoea.

Since pathogen inhibition is one of the modes of action of multispecies probiotics, several pathogen associated disorders may be prevented by the use of multispecies probiotics.

Method

Winclove Bio Industries has tested the pathogen inhibition capacity of several probiotic strains using the, in literature well described, well diffusion test [2-4]. A nutritious medium is poured into a petri-dish. In this agar medium a potentially pathogenic organism is grown. The probiotic strain is added to the hole in the agar. If the probiotic strain inhibits the pathogen, a clear zone is shown around the hole. The diameter is of this clear zone is measured (figure 2). The larger this zone, the better is the capacity of the probiotic strain to inhibit the pathogenic organism.

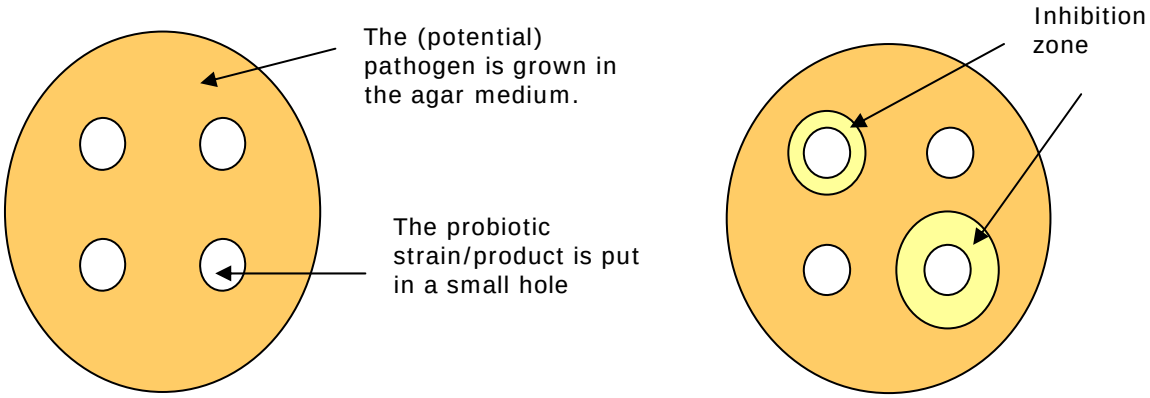


Figure 2: above; schematic overview of the well diffusion pathogen inhibition test. The inhibition zone is a measurement for the inhibition capacity of the probiotic strain against a specific pathogen. Below; picture of an agar plate with an example of weak and strong inhibition.

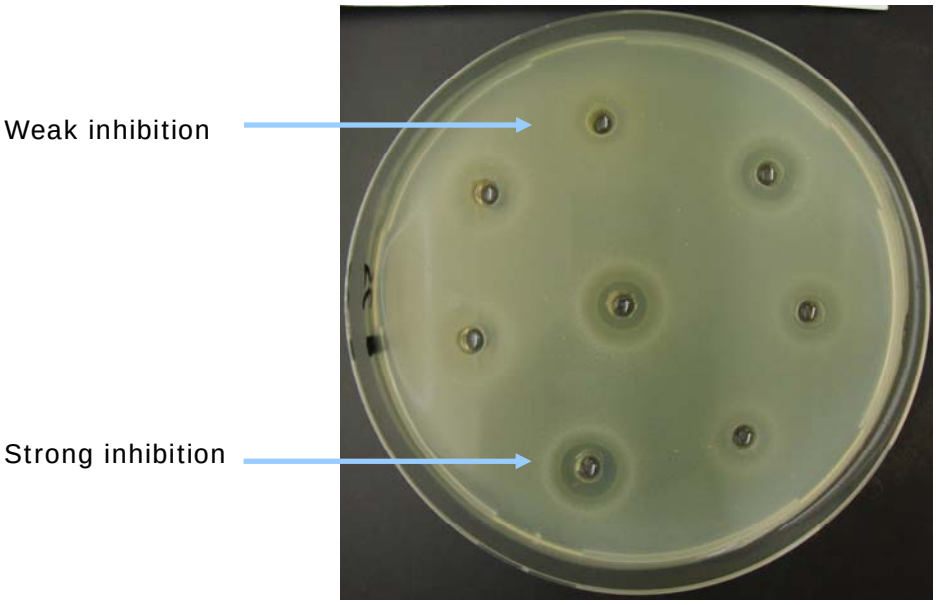


Figure 3 Example

Results

We have tested the strains of your products on their ability to inhibit the growth of four pathogens: *Escherichia coli, Salmonella enteritidis, Shigella* spp and *Pantoea agglomerans*. Below the relation of the pathogens to different diseases is explained and at the end the results of the inhibition tests are shown.

Escherichia coli

Escherichia coli (*E. coli*) is an important member of the normal intestinal microbiota of humans and other mammals. Apart from being a harmless intestinal inhabitant, it can be highly versatile and a, frequently deadly, pathogen. It can cause diverse intestinal and extra intestinal diseases.

Some types of *E. coli* can cause **infectious diarrhoea** or **food poisoning**. This can occur via contamination of meat or poultry while it is being processed, via water used for growing or shipping that contains manure or human waste, or it can get into food by unsafe handling or preparation in restaurants, grocery stores or at home.

E. coli can cause **Travellers' Diarrhoea (TD)**, which is a common illness affecting travellers. Each year between 20-50% of international travellers, an estimated 10 million persons, develop diarrhoea. Travellers' diarrhoea is largely caused by detectable and undetected bacterial enteropathogens[5]. *E. coli* causes the majority of TD cases, about 25-45%[6].

Urinary tract infection (UTI) is one of the most common bacterial infections in women, and one in four of these women will develop a recurrence. Various risk factors predispose women of different age groups to recurrence. Of the different pathogens, *E. coli* is the organism most commonly isolated in 70–95% cases[7].

E. coli was also shown in cases of **Antibiotic-Associated Diarrhoea** (AAD), diarrhoea that occurs when antibacterial medications (antibiotics) upset the balance of good and bad bacteria in your gastrointestinal tract. Antibiotic-induced perturbations of the intestinal microbiota can disturb colonisation resistance and have been associated with overgrowth of several pathogens. Most AAD infections are caused by *Clostridium difficile*, but also *E. coli* was found in several cases[8].

In cases of **Pouchitis** there was an increase found in the numbers of *E. coli*. Pouchitis is the major long-term complication after ileal pouch-anal anastomosis for ulcerative colitis (UC). It is only seen in patients with underlying UC, almost never in other cases where a pouch was placed. Together with the fact that the complication responds to antibiotic treatment, this suggests an infectious etiology in genetically susceptible inflammatory bowel disease (IBD) patients. However, there has been no single pathogen found to be solely responsible for this disease process. Although most research report increased numbers of *Clostridia*, Gosselink *et al* found a significant increase in *E. coli* in patients with pouchitis[9]. This suggests that there might be a relation between *E. coli* and pouchitis.

There are two forms of **inflammatory bowel disease** (IBD): Crohn's disease (CD) and ulcerative colitis (UC). They have several signs and symptoms in common, but they are very different conditions. One of the main differences between CD and UC is the location of the disease. CD can affect the digestive tract anywhere between the mouth and the anus, while UC only affects the large intestine (or colon). A second important difference is that CD inflammation involves all layers of the intestinal wall and UC affects only the inner lining[10].
In several articles, the presence of adherent-invasive *E. coli* in **Crohn's disease** is described. This *E. coli* seems to be associated specifically with the ileal mucosa in CD [11-14].

Infections caused by *E. coli* have been reported to increase the risk for **Irritable Bowel Syndrome** (IBS) [15-16]. IBS is a functional bowel disorder characterized by chronic abdominal pain, discomfort, bloating, and alteration of bowel habits in the absence of any detectable organic cause. Also diarrhoea and/or constipation can occur.
IBS may begin after an infection. An episode of acute enteric infection involving extra intestinal organs can lead to chronic complications and trigger IBS [17].

An other disease that is caused by *E. coli* is **Hemolytic Uremic Syndrome** (HUS). HUS is a disease that is characterized by acute renal failure and low platelet count among other things. It affects amongst 10% of patients infected with enterohemorrhagic *E. coli*, mostly young children and is therefore the most common cause of acute renal failure in children [18].

E. coli can also cause **meningitis**. This type of meningitis is much more common in infants than in adults. Risk factors in both children and adults include: local infection, brain surgery, recent injury to the head and urinary tract infections[19]. Many people recover completely, but a large number of people have permanent brain damage or die from this type of meningitis. Between 40% and 80% of patients with gram-negative meningitis do not survive, although these numbers may be improving.

In summary, *Escherichia coli* has been associated, besides food poisoning, with travellers' diarrhoea, antibiotic-associated diarrhoea, pouchitis, Crohn's disease, irritable bowel syndrome, haemolytic uremic syndrome and meningitis. We have tested the strains of the Progastro products on their ability to inhibit the growth of *E. coli in vitro* (see figure 3 to 5) .

Salmonella spp.

Salmonella spp. is group of well known pathogens. It causes infections in different cases.

Salmonella is the most common cause of **food poisoning** or **infectious diarrhoea**. It occurs after consuming food or water that is contaminated. Well known foods that are a risk for contamination are turkey, chicken or undercooked eggs.

Salmonella spp. is one of the causes of **Travellers' Diarrhoea** (TD). Although it is not as important as *E. coli*, it is responsible for 5-10% of the cases of TD worldwide [5-6].

Salmonella spp. is also associated with **Inflammatory Bowel Disease** (IBD), Crohn's disease (CD) and ulcerative colitis (UC). The role of pathogenic bacteria in the onset of these two conditions in not yet well described, however there are indications that some pathogens are associated.
Infectious agents causing an episode of infectious gastroenteritis could play a role in the initiation and/or exacerbation of IBD. It has been observed that following epidemics of *Salmonella* a small percentage of patients develop typical IBD [20].
The population-based cohort study performed by Gradel *et al*, showed an increased risk of IBD in individuals notified in laboratory registries with an episode of *Salmonella* gastroenteritis[21].
An other study showed that *Salmonella* infection led to an elevated risk for developing ulcerative colitis[17].

Salmonella infections are found to be associated with the development of **Irritable Bowel Syndrome** (IBS) [15-16]. Infections with *Salmonella* are reported to increase the risk for IBS.

Little is known about the role of pathogens in **constipation**. It is however described as a complication after *Salmonella* infection [22]. Also, constipation can be a symptom of IBS.

Salmonella has also been associated with the development of **reactive arthritis**. Arthritis is a group of conditions involving damage to the joints of the body. One of these conditions is reactive arthritis, which is an autoimmune disease that develops in response to an infection in another part of the body.
Ternhag *et al* found an increased risk in developing reactive arthritis within one year after infection with *Salmonella* among others [17].

Salmonella spp can also cause **Hemolytic Uremic Syndrome** (HUS). It is the most common cause of acute kidney failure in children and often occurs after gastrointestinal infections[23].

Finally, although it is very rare, *Salmonella* can cause **meningitis**. It causes less than 1% of the cases of bacterial meningitis. Those affected are mostly newborn babies, but cases may also occur in immunodeficient adults. [24]

In summary, *Salmonella* has been shown to be associated, besides food poisoning, with travellers' diarrhoea, irritable bowel disease, irritable bowel syndrome, constipation, reactive arthritis, haemolytic uremic syndrome and meningitis. We have tested the strains of your product on their ability to inhibit the growth of *Salmonella enteritidis in vitro* (see figure3 to 5).

Shigella spp.

Shigella spp. is an other common human pathogen and it can cause many infections. It is spread from an infected person to contaminate water or food, or directly to another person. *Shigella* can cause **infectious diarrhoea** or **food poisoning**.

Shigella spp. has been known as one of the main causes of **Travellers' Diarrhoea**, after *E. coli,* and it is, like *Salmonella*, responsible for 5-10% of the cases of TD [5-6].

Shigella could play a role in the onset of **Inflammatory Bowel Disease** (IBD). Following epidemics of *Shigella*, amongst other pathogens, a small percentage of patients develop typical IBD [20]. This could indicate that *Shigella* infections can increase the risk of development of IBD.

The same was shown in cases of **Irritable Bowel Syndrome** (IBS). *Shigella* could increase the risk of developing this disorder [15-16].

Shigella spp. infections can lead to **Hemolytic Uremic Syndrome** (HUS), a form of kidney failure[25]. Most cases occur in children, but all age groups can be affected.

Up to 40% of children with severe *Shigella enteritis* develop **neurological problems** including brain disease (encephalopathy) with headache and stiff neck amongst others [26].

Shigella spp. infections have also been associated with **reactive arthritis**. Reactive arthritis (ReA) is an inflammatory arthritis that arises after certain gastrointestinal or genitourinary infections[27-28]

In summary, *Shigella* can cause food poisoning and has been described in several articles to be associated with travellers' diarrhoea, irritable bowel disease, irritable bowel syndrome, hemolytic uremic syndrome, neurological problems and reactive arthritis. We have tested all the strains of ProGastro probiotics on their ability to inhibit the growth of *Shigella spp* (see figure3 to 5).

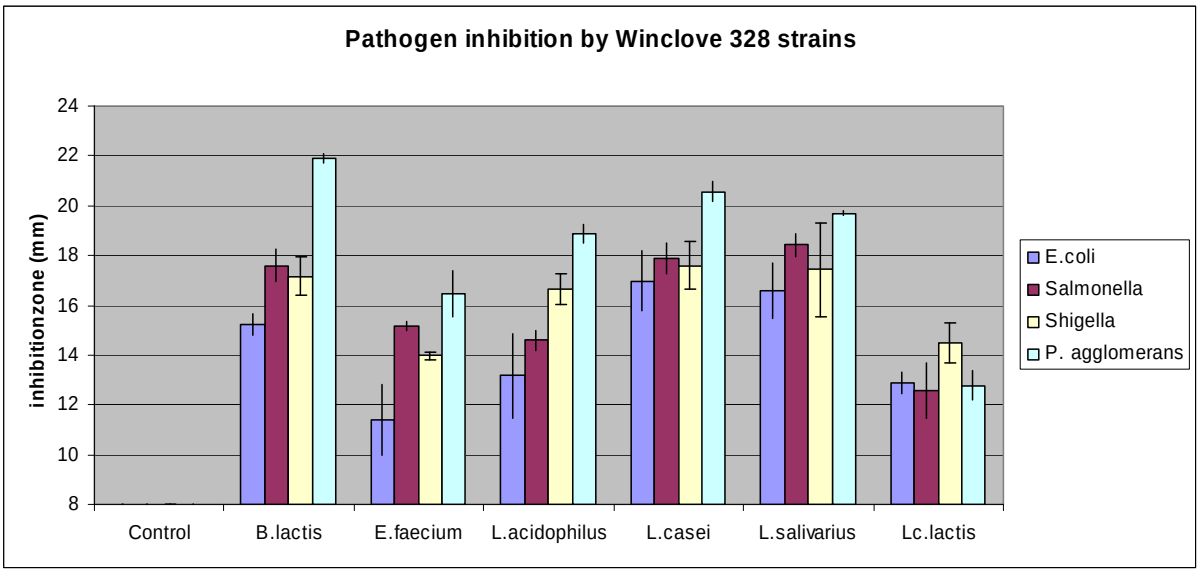
Pantoea agglomerans

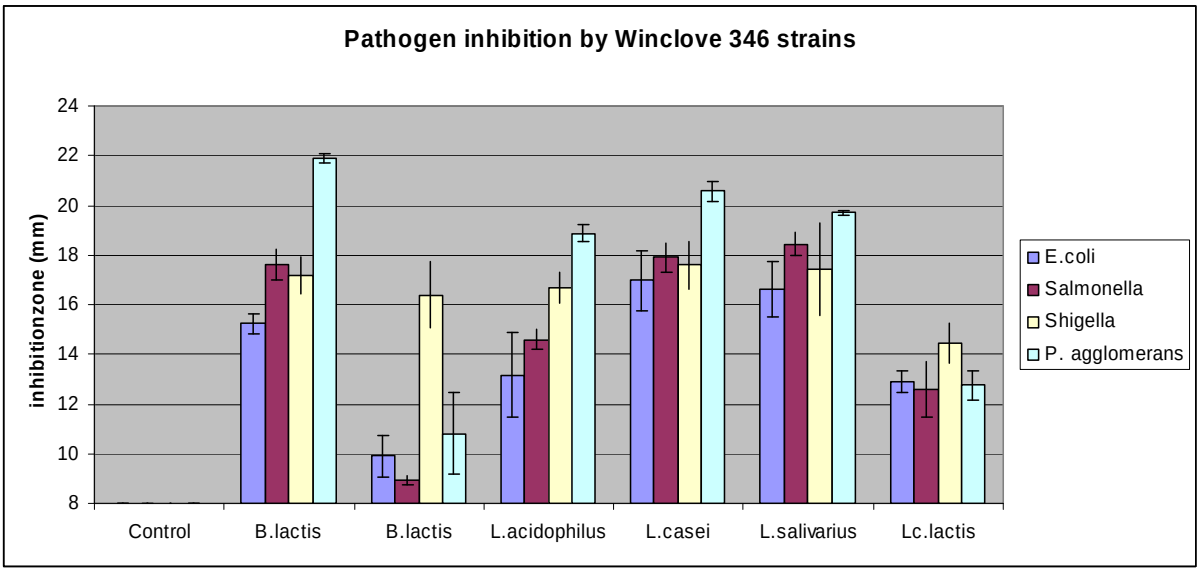
Pantoea agglomerans was formerly known as *Enterobacter agglomerans*, which is mainly reported in cases of infections after trauma by vegetation. **Soft tissue and/or bone and joint infections** can occur after this trauma.
Cruz *et al* reported cases of **septic arthritis** in children, after infection with *Pantoea agglomerans*. This indicated that infection with *Pantoea agglomerans* increases the risk of developing a form of arthritis [29].
Pantoea agglomerans can cause **infections of the urinary tract** and **blood stream infections** related to the presence of medical devices such as urinary catheters and intravenous lines[29].

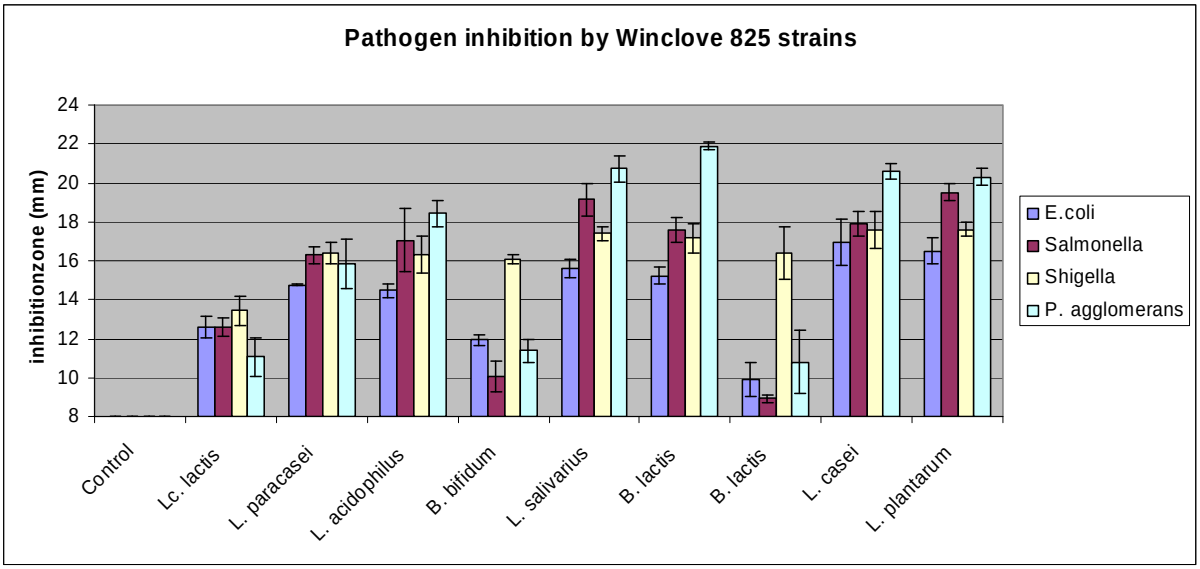
We have tested the strains of your products on their ability to inhibit *Pantoea agglomerans in vitro* (see figure3 to 5)

Results of inhibition tests

The graphs below show the inhibition zones created by the different strains of the ProGastro products. The results are shown per product, in each graph you see the inhibition zones produced by each strain, for the four previously described pathogens. The negative control shows no inhibition (8 mm), where the strains show inhibition zones of 10 to 22 mm approximately depending on the pathogen. This indicates that all strains can inhibit the growth of *E. coli, Salmonella, Shigella and Pantoea agglomerans in vitro*.






Pathogen inhibition by Winclove 825 strains
inhibitionzone (mm)
24
22
20
18
16
14
12
10
8
Control
Lc. lactis
L. paracasei
L. acidophilus
B. bifidum
L. salivarius
B. lactis
B. lactis
L. casei
L. plantarum
E.coli
Salmonella
Shigella
P. agglomerans

Conclusions

Winclove 328

All the strains in Winclove 328 were tested for their ability to inhibit the pathogens *in vitro*.

	Application	Strains	Results
Escherichia coli	Infectious diarrhoea Travellers' diarrhoea Antibiotic-associated diarrhoea Pouchitis Inflammatory bowel disease (IBD) Irritable bowel syndrome (IBS) Hemolytic Uremic Syndrome (HUS) Meningitis	B. lactis E. faecium L. acidophilus L. casei L. salivarius Lc. Lactis	+ +/- +/- + + +/-
Salmonella spp	Infectious diarrhoea Travellers' diarrhoea IBD IBS Reactive arthritis HUS Constipation Meningitis	B. lactis E. faecium L. acidophilus L. casei L. salivarius Lc. Lactis	+ + + + ++ +/-
Shigella spp	Infectious diarrhoea Travellers' diarrhoea IBD IBS HUS Reactive Arthritis	B. lactis E. faecium L. acidophilus L. casei L. salivarius Lc. Lactis	+ +/- + + + +
Pantoea agglomerans	(Septic) arthritis Urinary tract infections Blood stream infections	B. lactis E. faecium L. acidophilus L. casei L. salivarius Lc. Lactis	++ + ++ ++ ++ +/-

Table 2; results per pathogen per strain from Winclove 328.

As is shown in table 2, the strains of Winclove 328 can all inhibit *E.coli, Salmonella, Shigella* and *Pantoea agglomerans.*
The results indicate that Winclove 328 can protect against infectious diarrhoea.
The strains of Winclove 328 show good inhibition against pathogen S*higella, Salmonella* and *E. coli*. This could give a protection against food poisoning. All three pathogens are a common cause of **TD** and associated with **IBD** and **IBS.** These results also indicate that the product can well be used as a preventative for **constipation** and **AAD** caused by *E. coli.* **Septic Arthritis** is associated with *P. agglomerans*. The strains of Winclove 328 have shown to be well able to inhibit this pathogen. **Reactive Arthritis** can be caused by *Samonella* and *Shigella*, which are inhibited by the strains in Winclove 328.

These results substantiate that Winclove 328 is a high quality product good for maintaining the intestinal balance and suitable for several target groups.

Winclove 346

Winclove 346 is a product specifically developed for children for supporting their intestinal microbiota. We have tested the strains present in Winclove 346 for their ability to inhibit pathogens associated with several applications. Table 3 shows the results per pathogen, per strain present in Winclove 346.

	Application	**Strains**	**Results**
Escherichia coli	Infectious diarrhoea Travellers' diarrhoea Antibiotic-associated diarrhoea Pouchitis Inflammatory bowel disease (IBD) Irritable bowel syndrome (IBS) **Hemolytic Uremic Syndrome (HUS)** **Meningitis**	B. lactis B. lactis L. acidophilus L. casei L. salivarius Lc. Lactis	+ +/- +/- + + +/-
Salmonella spp	Infectious diarrhoea Travellers' diarrhoea IBD IBS Reactive arthritis **HUS** **Constipation** **Meningitis**	B. lactis B. lactis L. acidophilus L. casei L. salivarius Lc. Lactis	+ +/- + + ++ +/-
Shigella spp	Infectious diarrhoea Travellers' diarrhoea IBD IBS **HUS** Reactive Arthritis	B. lactis B. lactis L. acidophilus L. casei L. salivarius Lc. Lactis	+ + + + + +
Pantoea agglomerans	(Septic) arthritis Urinary tract infections Blood stream infections	B. lactis B. lactis L. acidophilus L. casei L. salivarius Lc. Lactis	++ +/- ++ ++ ++ +/-

Table 3; results per pathogen per strain from Winclove 346.

As can be seen in Table 3, the strains in Winclove 346 are good in inhibiting pathogens associated with **TD**, **IBS** and **IBD.** *Salmonella* is also associated with the initiation of **constipation**. Constipation is a common problem in children and these results indicate that Winclove 346 could contribute to preventing the initiation of constipation. The results furthermore show that Winclove 346 could well be used in combination with antibiotics, since it shows good inhibition against *E.coli,* which can be a cause of **Antibiotic-associated diarrhoea**. *E. coli* is also significantly increased in patients with **Pouchitis**, however, pouchitis is not common in children. **Septic Arthritis** is linked

with *Pantoea agglomerans*, an infection with this pathogen increases the chance on septic arthritis. The strains in Winclove 346 show strong inhibition against this pathogen. **Reactive arthritis** on the other hand is associated with infections with *Salmonella* and *Shigella*. Both pathogens are well inhibited by the strains in Winclove 346

The results also indicate that Winclove 346 could protect against **infectious diarrhoea** or **food poisoning**, for which young children have a higher risk.

Meningitis is a life threatening disease, which can occur after infection with *E. coli*, *Salmonella* and/or *Shigella*, mostly in children, although the relation between the pathogens and meningitis is not strong. Preventing these infections in children with Winclove 346 could help to prevent the onset of meningitis.
Winclove 346 could also help to prevent the development of **Hemolytic Uremic Syndrome**, which is the most common cause of renal failure in children and is mostly caused by gastrointestinal infections with *E. coli, Shigella* and also *Salmonella*.

Overall, it can be concluded that the strains in Winclove 346 show a good to very good inhibition to some common pathogens associated with several disorders. Winclove 346 is a high quality probiotic which is good in balancing the microbiota of children and contributing to their intestinal health. Based on the results it can be concluded that Winclove 346 can prevent the growth and possible colonization of these pathogens and could hereby prevent disorders associated with the tested pathogens.

Winclove 825

For the product Winclove 825, mainly the results of E. coli, Salmonella spp and Shigella spp inhibition are important, because of their relation with IBD and IBS.

Overall, the following results were shown within the pathogen inhibition tests. A summary of the results for the product Winclove 825 is given in the table below.
(results are indicated with – and +, based on results of the whole experiment:
No inhibition - = 0 to 8 mm, moderate inhibition +/- = 8 to 14 mm, good inhibition + = 14 to 18 mm, very good inhibition ++ = 18 mm or more)

	Application	**Strains**	**Results**
Escherichia coli	Infectious diarrhoea Travellers' diarrhoea Antibiotic-associated diarrhoea Pouchitis **Inflammatory bowel disease (IBD)** **Irritable bowel syndrome (IBS)** Hemolytic Uremic Syndrome (HUS) Meningitis	Lc. Lactis L. paracasei L. acidophilus B. bifidum L. salivarius B. lactis B. lactis L. casei L. plantarum	+/- + + +/- + + +/- + +
Salmonella spp	Infectious diarrhoea Travellers' diarrhoea **IBD** **IBS** Reactive arthritis HUS Constipation Meningitis	Lc. Lactis L. paracasei L. acidophilus B. bifidum L. salivarius B. lactis B. lactis L. casei L. plantarum	+/- + + +/- ++ + +/- + ++
Shigella spp	Infectious diarrhoea Travellers' diarrhoea **IBD** **IBS** HUS Reactive Arthritis	Lc. Lactis L. paracasei L. acidophilus B. bifidum L. salivarius B. lactis B. lactis L. casei L. plantarum	+/- + + + + + + + +
Pantoea agglomerans	(Septic) arthritis Urinary tract infections Blood stream infections	Lc. Lactis L. paracasei L. acidophilus B. bifidum L. salivarius B. lactis B. lactis L. casei L. plantarum	+/- + ++ +/- ++ ++ +/- ++ ++

Table 4; results per pathogen per strain from Winclove 825.

The table shows that all strains in Winclove 825 are able to inhibit several important pathogens. Several strains show a good inhibition to E. coli. Some strains show even a very good inhibition against Salmonella and also Shigella can be inhibited by the strains of Winclove 825. These results indicate how Winclove 825 could help against IBD and IBS and explain a possible working mechanism of the product.

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