Fighting fire with fire: Probiotics as an alternative to antibiotics

Karin Hedin
Populärvetenskaplig sammanfattning av Självständigt arbete i biologi 2013
Instutionen för biologisk grundutbildning, Uppsala universitet

The discovery of antibiotics in the early 20th century marked a new era in the field of medical science, and changed the fate of thousands of people in the newly industrialized western world. Disease caused by bacterial infections had long proven a difficult task for the scientific society and the mortality rates were high. In addition, the medicines available often posed a threat to the patient's own health, being either too strong or of toxic substances, or could at best offer some relief for the symptoms. To cure the sickness and rid the patient of the disease altogether was rare. Antibiotics proved a new mean to heal those who had succumbed to illness caused by infection and the idea that we had stumbled upon what appeared to be a miracle treatment prevailed for many decades. However, with the coming of antibiotics followed the first resistant bacterial strains – bacteria that through natural selection had survived the wipe-out process and through replication continued to spread. With this new knowledge, a desperate search for new antibiotics began, which may be considered as one of medical science's greatest challenges and still today has not been met. As research progresses, the task becomes more difficult to master, due to the fact that the answers demand more advanced science. To surpass what Mother Nature once so perfectly fashioned appears to be an exceedingly difficult task. How then do we continue this ongoing battle? Will the answer lie in what appears to be an already exhausted field of research, or is it time we looked for new ways in which to tackle the problem at hand? New discoveries suggest that we look to bacteria itself to find a cure and that we exploit the possibilities that come with this new notion. Indeed, perhaps the solution does not lie with the finding of a new antibiotic medicine, but instead within the prospect of harnessing bacteria to be used as a weapon? Perhaps the time has come to fight fire with fire?

Man and microorganism

The relationship between man and microorganism goes back to our beginning, when we were little more than one-celled beings. To comprehend the role that bacteria have in our modern society, we must understand the importance of co-evolution - a process sprung over a vast space of time that inevitably has shaped the genetics of both parts. The bacteria living upon our skin and inside our bodies constitute for three times the number of human cells. While many hold the potential of being pathogenic, for example those inhabiting the compartments of the nostrils, a large number are bacteria that actually benefit the host organism, and may even be essential to its' survival. Microorganisms belonging to the latter category primarily colonize the epithelial walls of the colon, where they produce anti-microbial metabolites as byproducts from digesting nutrients that pass through the organ. These substances are often organic acids known as lactic acids. When discharged into the lumen of the colon, they act by lowering the pH of the environment and consequently exert an inhibitory effect on the growth of bacteria lacking an adaptation to such surroundings.

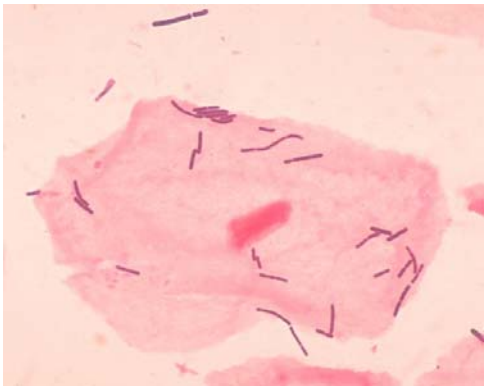
Bacteria living in the colon compose the microflora of the host organism. Several attempts have been made to categorize the variety of species residing in the colon, and although it is

certain that the majority of bacteria are anaerobic, meaning that they require no oxygen in order to grow and prosper, it is a domain in progress of being charted. However, through sequencing of bacterial genomes, it has become apparent that bacteria belonging to the genera of *Bacterioides, Eubacterium, Bifidobacterium, Peptococcus, Clostridium* and *Peptostreptococcus* are among the most commonly found microorganisms in the gut, whereas *Escherichia coli, Enterobacter, Lactobacillus* and *Enterococcus* represent a minority in comparison. In recent years scientists have focused on exploring to what extent the composition of the microflora affects the host's immune system. New discoveries suggest that individuals lacking a complete flora are more inclined to succumb to illness caused by infection if exposed to harmful bacteria, than people with a normal microflora. These findings suggest that the microflora is of great importance to our immune system. Although the colon naturally contains bacteria that are both harmless and potentially pathogenic, the latter group does not exercise a threat unless the balance is compromised.

The discovery of probiotics

Based on what we know today about the bacteria living inside the human system, and their abilities to modulate the microflora through production of organic acids, scientists have begun to explore the possibilities of using bacteria as a means to fight infections. However modern this notion may seem, the idea of harnessing the power of microorganisms for our own benefit, dates back to the beginning of the 20th century and to the scholar Elie Metchnikoff. During one of his travels to Bulgaria, he made the observation that fermented milk appeared to have beneficial effects on the health of the country´s peasants, who displayed an unusual vitality and fitness, and were less often taken ill by sickness. Years later, while working in a pasteurizing company, he concluded that the favorable properties of the products could be credited to the microorganisms living and thriving in the milk, somehow affecting the health of the consumer.

These microorganisms were later given the name probiotics, which literally means "for life". The name encompasses bacteria which exert a positive effect on the consumer's health by modulating the balance of the microflora. A great number of these bacteria are able to ferment carbohydrates thus producing lactic acid in the process, in the same manner as the bacteria colonizing the gut. A common characteristic among bacteria classified as probiotic is that they are of host origin, meaning that they belong to any of the species normally found in the human colon. Consequently, species belonging to the families *Streptococcus, Enterococcus, Bifidobacterium* and *Lactobacillus* are frequently employed in the production of probiotics, where the latter genera perhaps is the most common. Even certain non-pathogenic strains of *E. coli* have been used for the same purpose. These are all considered to be safe in regards to the host organism's health and lack traits that could render the bacteria pathogenic.



The picture displays bacteria of the genera *Lactobacillus*, residing in the vicinity of a human epithelial cell (Wikimedia Commons 2013).

The characteristics of probiotic bacteria and their uses

In addition to producing substances that contribute to the acidification of the environment, lactic acid bacteria function in a wide variety of ways. Their ability to colonize the gut can be ascribed to their capacity of adhering to receptors in the epithelial cell walls. By claiming such receptors, they compete with other, potentially hostile bacteria, about the available space. Competition regarding nutrients also occurs. Although the colon is abundant in food resources, it only requires for one essential substance to become scarce, for bacteria to be unable to sustain themselves. Moreover, results from several studies suggest that certain gut-inhabiting microorganisms are able to stimulate the immune system of the host organism, inducing a higher cell count of natural killer cells (NK cells) as well as macrophages. There is also evidence proposing that lactic acid bacteria can stimulate certain epithelial cells into increasing the production of mucus, which results in a thicker coating lining the walls of the lumen. This mucous membrane functions primarily as a barrier between bacteria and cell receptors, thus inhibiting colonization by harmful microorganisms as well as reducing the risk of developing an infection.

The positive effects accompanying the intake of probiotics, both as a prophylaxis or as a treatment of disease, are well-documented. Results from a study from 2004 display the healing effects of probiotics on patients suffering from ulcerative colitis, an inflammatory bowel disease resulting in hemorrhage of the colon and severe diarrhea. By prescribing probiotics containing a strain of *E. coli* called Nissle 1917, several of the symptoms normally associated with the affliction were relieved. In addition, the treatment with *E. coli* Nissle 1917 appeared to be equally effective as the conventional, anti-inflammatory medicine Mesalazine. Yet another experiment was conducted with *L. rhamnosus GG,* where similar results could be observed, and confirms the efficacy of probiotics as an alternative to conventional medicine in the treatment of ulcerative colitis. Research concerning the influence of probiotics on irritable bowel syndrome (IBS) further suggests the possibilities of using probiotics as a curative for inflammatory colon diseases. Experiments carried out with the probiotic bacteria *L. plantarum* 299v have been particularly successful in relieving patients affected with irritable bowel syndrome of their symptoms.

There are also data supporting the beneficial effects of probiotics in suppressing disease related to bacterial and viral infections in the colon. Prescription of probiotics containing *L. rhamnosus* GG resulted in ridding 84 percent of the patients in a test-group of diarrhea, caused by an infection of the highly pathogenic bacteria *C. difficile*. Similar results could be observed after treating patients suffering from the same type of infection, with a mixture of bacterial cultures consisting of *L. casei, L. bulgaricus* and *S. thermophilus* during a study in 2007. Diarrhea as a result of infection by rotavirus, which is one of the most common causes of gastric influenza in the industrialized world, could be repressed by the use of the probiotic strains *L. rhamnosus* GG, *L. reuteri*, *L. casei* Shirota and *B. lactic* Bb12 in a study from 2013.

Studies demonstrating the inhibiting effects of lactic acid bacteria on the development of gastric ulcers, can also be found. Infection of the gastric-living bacteria *Helicobacter pylori* is a common cause behind the development of ulcers as well as stomach cancer. Research has demonstrated that probiotic bacteria effectively can arrest production of urease - an enzyme that through a series of reactions lowers the pH of the environment to a level which makes it possible for *H. pylori* to sustain itself in the gastric cavity. When the ability to produce urease ceases to exist, the bacteria die as a consequence and the risk of infection is reduced.

There is also evidence that probiotics may be used as a preventative for developing allergies and conditions of hypersensitivity, such as lactose intolerance. Although the details behind these mechanisms remain to be discovered, some scientists have suggested that it may be the bacteria's ability to produce lactase, an enzyme accountable for the breaking down of lactose, that is responsible for the observable relief in symptoms accompanied by the intake of probiotics.

Can probiotics replace antibiotics?

However forceful these substances may appear, the question still remains whether they may be able to successfully replace antibiotics in curing diseases caused by infection. Although what type of medicine to use may be determined by the severity of the infection, there is a number of possible scenarios where probiotics may be more appropriate as a curative than antibiotics.

Bacterial vaginosis is one of the most common infections among women. It affects the vaginal tract and is usually the result of a disturbance of the vaginal microflora. When harmless bacteria normally colonizing the area are wiped out, due to an over excessive use of spermicides, antibiotics or because of hygiene routines, the result is usually an overgrowth of pathogenic bacteria, such as *E. coli*. The prescribed treatment is often the antibiotic substance Metronidazole. Although useful against anaerobic bacteria in general, it has a surprisingly low efficacy against two of the most common bacteria associated with bacterial vaginosis - *Gardnerella vaginosis* and bacteria of the *Mobiluncus* species. Moreover, treatment with antibiotics tend to cause an unbalance in the microflora, thus inducing the risk that new infections develop and is commonly associated with a variety of undesired side effects. In contrast, probiotic bacteria work by competing with harmful bacteria over adhesion points in the epithelial walls as well as by lowering the pH of the surroundings. In a study from 1992, patients with bacterial vaginosis were prescribed probiotics of the sort *L. acidophilus* for 6 days. At the end of the experiment, 43 percent of the participants experienced a relief of symptoms, which can be compared to the placebo group, where no difference in health condition could be measured.

Infection by the pathogenic bacteria *E. coli* 0157:H7 is one of the most common causes behind stomach illness, normally associated with symptoms such as diarrhea and vomiting. When colonizing the gut, *E. coli* 0157:H7 discharges a toxin, which in high concentrations may lead to a rare but serious complication known as hemolytic uremic syndrome (HUS). The disease is characterized by renal failure and anemia, which in 3-5 percent of the victims result in death. Common stomach illness however is relatively harmless, and is often treated with antibiotics. Nevertheless, studies have shown that certain substances of antibiotics may work by stimulating toxin discharge in *E. coli* 0157:H7, thus increasing the risk of developing hemolytic uremic syndrome. Although this outcome is unusual, it may be enough to rethink the use of antibiotics as the self-evident medication for infection caused by *E. coli* 0157:H7.

The use of probiotics is not restricted to humans exclusively. In the animal breeding industry, the conventional medicine for treating infections has been antibiotics. For example, when suppressing outbreaks of diarrhea in weaning pigs, antibiotics are prescribed both as a preventative against infections as well as a curative. Although ridding the animal of infection often calls for more than one brand of antibiotics, which in turn prolongs the period of

treatment and contributes to the development of resistant bacteria, the use of antibiotics in animal breeding has continued nonetheless. Research has shown that probiotics may be just as effective or even more so than antibiotics in this matter. Moreover, probiotics can be used as a safe prophylaxis. Preventative use of antibiotics may comprehend giving the animals medicine for every day during a period of several years. This may, although somewhat contradictory to the original purpose, compromise the animals' health and result in the formation of chemical reservoirs in nature. Use of probiotics does not bring about the same cascade of consequences, and is therefore a better alternative to antibiotics.

Even if probiotics generally are considered safe, exceptions should be made concerning their uses. In patients with severe, life-threatening infections, it is difficult to foresee the consequences of prescribing live bacterial cultures. However seldom it may occur, there are documented cases in medical history where patients have developed infection due to the intake of probiotics, resulting in the worsening of condition. This has primarily happened to individuals suffering from a serious illness accompanied by an impaired immune system. One medical area where the attempts have been made to replace antibiotics with probiotics is patients afflicted with hepatic encephalopathy. This illness is characterized by a dysfunction of the liver, which in some cases result in the organ having to be transplanted. The underlying cause of the sickness is the accumulation of toxic substances in the blood, which can be accounted for by pathogenic bacteria inhabiting the gut. For this reason, probiotics have been used in order to suppress the growth of such bacteria. However, hepatic encephalopathy often affects the patient's general health to such a degree that the immune system may not be able to fight back any potential outbreak of infection caused by probiotic bacteria. Therefore, in this case antibiotics should be relied upon as the natural choice of treatment, and the role of probiotics should be strictly prophylactic, used in order to prevent the illness from becoming too severe. This is also true of people suffering from ulcerative colitis, which also represent a medical field where attempts to replace antibiotics with probiotics have been made. As with hepatic encephalopathy, patients suffering from ulcerative colitis sometimes tend to develop a weakening in the immune system. Although treatment with probiotics have been successful, thus inspiring hope that probiotics in the upcoming future may be the self-evident choice of treatment for such a disorder, the patient's general condition should be taken into account before deciding on what medicine to use.

In conclusion, it appears that areas of medicine do exist where probiotics successfully can replace antibiotics. For the first time in almost a century, there is an urgent need to find new solutions in order to eradicate an old problem. The race in finding new medicines is coupled with the development of resistant pathogenic strains, and the demands that science moves faster are high. Perhaps probiotics is not the only answer, but it is, to a certain degree, an answer nonetheless. As Albert Einstein once so eloquently put it, "Everything must be made as simple as possible", and perhaps fighting bacteria with bacteria is doing just that.

Further reading

Hedin K. 2013. Probiotika - lösningen på antibiotikarelaterad problematik? Självständigt arbete i biologi, Uppsala Universitet.

Saad N, Delattre C, Urdaci M, Schmitter JM, Bressollier P. 2013. An overview of the last advances in probiotic and prebiotic field. LWT - Food Science and Technology **50**: 1-16.

Wikimedia Commons. 2013. WWW-dokument: http://commons.wikimedia.org/wiki/ File: Lactobacillus_ sp_01.png. Date visited 17 March 2013.