

## The history of probiotics: the untold story

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Received: 20 July 2014 / Accepted: 26 September 2014

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### REVIEW ARTICLE

#### Abstract

Probiotic, a word derived from Latin, means 'for life.' A long time before the awareness of probiotic microorganisms, fermented products, such as beer, bread, wine, kefir, kumis and cheese had been very frequently used for nutritional and therapeutic purposes. It is widely believed that fermented products were probably found, or better to say, discovered spontaneously. The legend tells that yoghurt is most likely resulted from a fermentation process within the animal skin bags used for transportation of water and milk in regions with low humidity and high temperatures (Middle Asia and Middle East). The history of probiotics goes parallel with the evolution of human race and, thanks to the sophisticated techniques at the moment, can be traced back to the ancient times, nearly 10,000 years ago. The aims of this review are to highlight the important events for probiotic history, to correct the widely available anonymous misinformation in the literature and to remind to the readers important characters in its history.

**Keywords:** history of probiotics, fermented products, Henry Tissier, Stamen Grigorov, Elie Metchnikov

#### 1. Introduction

Several medical and popular sources have indicated that the first use of probiotics in the history of humanity dates back to 2000 BC when man first discovered how to preserve milk for longer periods. The first food-makers actually transformed the milk into fermented dairy products using bacteria and yeasts, although unaware of their existence (Nakazawa and Hosono, 1992). People have used fermented products to recover from certain diseases for two principal reasons; they are very nutritive and contain live microorganisms that are able to combat certain infections.

However, recent scientific papers have clarified that our ancestors were already using yeasts in the production of beverages much earlier than 2000 BC (Sicard and Legras, 2011). Based on the relicts of ancient Egypt, it can be seen that the fermented dairy products 'Laban Rayad' and 'Laban Khed', which are still common in the present-day Middle East, were in use as early as 3500 BC (Abou-Donia, 2008). With contemporary sophisticated techniques in molecular archeology, they have now been traced back to nearly 10,000 years ago.

Over the course of human history, using a system of trial and error and careful observation, different cultures began producing fermented beverages (Godoy *et al.*, 2003). At the time, people knew that leaving fruits and grains in covered containers for a long time produced wine and beer, but no one fully understood why the recipe worked. The process was named fermentation, from the Latin word 'fervere', which means 'to boil.' The name came from the observation that mixtures of crushed grapes kept in large vessels produced bubbles, as though they were boiling. Producing fermented beverages was tricky. If the mixture did not stand long enough, the product contained no alcohol, but if left for too long, the mixture rotted and was undrinkable. Through empirical observation, people learned that temperature and air exposure are key to the fermentation process (Alba-Lois and Segal-Kischinevzky, 2010).

More recently, in 1856, a man who was producing alcohol from sugar beetroot fermentation sought Pasteur's help because he was having problems at his distillery. He was obtaining a substance similar to sour milk instead of alcohol. Pasteur analysed the chemical contents of the sour substance and found that it contained a substantial amount

of lactic acid. When he compared the sediments from different containers microscopically, he noticed that large amounts of yeast were visible in samples from the containers in which alcoholic fermentation had occurred. In contrast, in the polluted containers, the ones containing lactic acid, he observed 'much smaller cells than the yeast.' Pasteur's finding showed that there are two types of fermentation: alcoholic and lactic acid. Alcoholic fermentation occurs through the action of yeast and lactic acid fermentation through the action of bacteria (Mazzarello, 2002).

There is much misinformation on the internet, in books and, unfortunately, even in scientific articles. These mistakes are the result of a 'copy and paste' system without a thorough search of literature. The aim of this manuscript is to clarify the history of both fermentation and probiotics with reference to recent scientific articles. In addition, the untold story of a physician will be brought to light to remind the scientific community who should actually be praised.

## 2. Ancient history

Looking back in time a few thousand years, there is much evidence of fermentation. The most exciting findings in the history of humankind have just been revealed from excavations in the city of Jiahu located in the southwestern part of the Chinese Republic. From an analysis of the findings, archaeologists reported that micro-organisms were used in the production of fermented beverages, even in 7000 BC (Zhang *et al.*, 1999). Molecular archaeologists from the University of Pennsylvania, working on one of the earliest examples of pottery, discovered that the first beer had been prepared from rice, honey and fruits with yeast used for fermentation (McGovern *et al.*, 2004).

During excavations in 1995, Prof. John Darnell of Yale University uncovered remains from the period of Scorpion I (3150 BC), the legendary first pharaoh of the Upper Egypt Dynasty. The papyri uncovered at the site indicated that wine had been mixed with herbs and used as a medicine for many years. For thousands of years, it has been widely believed that the god Osiris was the first to invent and drink wine (Darnell and Darnell, 2007). However, this is not a scientific fact. According to a recent book by Prof. Patrick McGovern of the world-renowned Archaeology Department of Pennsylvania University, wine was first produced in Georgia around 6000 BC (McGovern and Fleming, 2007). The earliest wine jars dating back to 5500 BC were uncovered during excavations on the Zagros Mountains in the west of Iran (PhysOrg, 2011). Similar findings of the same period have been found during other excavations in the northern part of the region, the so-called 'Fertile Crescent', which includes southern parts of the Caspian Sea and territories of Armenia, Northeastern Turkey and Northwestern Iran (McGovern, 2005).

Furthermore, a building presumed to be 6,000 years old, which was uncovered by an archaeological study in a cave in Armenia in 2007, was reported to be the earliest wine-making facility on the University of California, Los Angeles website (UCLA, 2011). All these areas in Caucasia are compatible with what the Bible says about Noah after landing the Ark on Mt Ararat: 'And Noah began to be an husbandman, and he planted a vineyard: and he drank of the wine, and was drunken' (King James Bible, Genesis, 9:20-21).

## 3. Theological history

Functional foods can be seen to have been often documented in holy inscriptions, beliefs and daily practices of various religions. Hinduism is the oldest world religion with origin and founder unknown. Indians call their religion 'Sanatana Dharma', which means the eternal or everlasting religion (Doniger, 2009). The holy scripture of this eternal religion, 'Holy Vedas' refers to the significance of fermented dairy products for health in daily life.

Based on the translations of Sumerian tablets, information on the fermentation of milk has been available since 2000 BC, with different recipes for cheese production by various methods (Hallo, 1972). Among the most interesting texts in Sumerian tablets is a poem on how to make beer, which is presumed to date from 3000 BC. This poem, entitled 'A Hymn to Ninkasi' according to an Oxford University translation, is a hymn or prayer to Ninkasi, the Sumerian Goddess of beverages, which describes the phases of beer brewing in order to pass the recipe down through the generations. As described in this tablet, bread as a starter (source of yeast) was added to hulled grains, then kept in fermentation tanks, and drained into a collecting jar (Oxford University, 2014).

Unfortunately, numerous internet pages and scientific articles still quote a 'Persian version of the Old Testament which states 'Abraham owed his longevity to the consumption of sour milk' (Genesis, 18:8). However, in the King James Authorised Version, Genesis 18:8 states 'And he took butter, and milk, and the calf which he had dressed, and set it before them; and he stood by them under the tree, and they did eat'. In this verse, Abraham serves three men who are actually angels bringing the good news that he will have a son. The Holy Prophet Moses also preached that yoghurt was a special food sent by the Lord to his tribe. It is known that wine has been used as a sedative and antiseptic after circumcision in the Jewish tradition. The Talmud has a passage stating 'Wine is at the head of all medicines; where wine is lacking, drugs are necessary' (Jewish Encyclopedia, 2014).

The ancient Greeks had a more systematic approach to medicine and used wine as therapy. The ancient Greek physician Hippocrates (460-370 BC), known as the father of

medicine, recommended wine as part of a healthy diet: 'Wine is fit for man in a wonderful way, provided that it is taken with good sense, by the sick as well as the healthy' (Sandler and Pinder, 2003). In periods before Hippocrates, the medicinal use of wine had been mentioned as an antiseptic, anesthetic, sedative, hypnotic, appetite stimulant, anti-convulsive, diuretic, purgative, antidiarrhoeal, antipyretic and anti-anemic (Robinson, 2006).

Fermented food products, particularly dairy products and wine, can be seen to have been in frequent use in daily life in Christianity (McGovern, 2007). Wine is significant in the Eucharist as a symbol of the blood of Christ and is symbolic of pledges made to share the fullness of life. Wine has certain properties that are sweet and bitter representing 'Life's Journey'.

On many occasions, beer has been a life-saver (Top Documentary Films, 2013). In the Middle Ages in Europe, low alcohol beer was brewed especially for sailors because fermented beverages were resistant to contamination. This feature made beer an essential drink on long sea voyages and during epidemics such as the plague. Saint Arnold of Metz (580-640) realised the importance of drinking beer instead of water during an outbreak of plague in Metz, France. Many Christian saints have advocated beer for medicinal purposes (Brookston Beer Bulletin website, 2014), particularly the following four saints with the approval of the Vatican:

- Luke the Apostle, the author of one of the New Testament Gospels was a physician born in ancient Antioch.
- Nicholas of Myra, better known as Santa Claus, lived in Patara, and died in 342 AD.
- Augustine of Hippo, born within the borders of present-day Algeria, was one of the most important figures in the establishment of the Roman Catholic Church (354-430).
- Saint Wenceslas, the founding king and patron saint of the Czech state (907-929).

## 4. History

The advent of written documents made it possible for us now to have more detailed and accurate information about the history of probiotics and humankind.

### Roman history

The Roman army commander, writer and philosopher, Pliny the Elder (23-79 AD) owes his reputation in history more to his encyclopedia entitled 'Naturalis Historia' than to his military victories (Wethered, 1937). It is one of the most widely-read, instructive works of reference in history. It represents a summary of all the information available until the day it was completed (76-77 AD) and is regarded as the first encyclopedia, comprising 169 chapters in 37 volumes. This monumental masterpiece makes a summary of more

than two thousand books of 400 ancient authors. In this colossal work, Pliny stated that 'The barbarians were able to thicken milk into a substance with a pleasant acidity and treated many diseases in the geographies he travelled until then' (Vandenplas, 2007). Based on the information in this encyclopedia, soured milk has been used for the treatment of diarrhea, and the treatment of vaginal discharge in the Palearctic region for thousands of years.

### Mongolian history

It is said that during the expansion period of the Mongolian Empire, founded by Ghengis Khan, a messenger arrived in a village prior to a desert crossing and asked to fill his water bag. Disgruntled by the Mongolian invasion, the villagers filled the bag with milk instead of water. When he became thirsty, the messenger noticed that he had a custard-like liquid in his bag, not water, but had no choice but to drink the liquid to slake his thirst. When this story became known to him, Ghengis Khan apparently added sour milk to the provisions list of his army. The Mongolian empire of Ghengis Khan became the largest contiguous territory in the world (22% of the Earth's total land area) (Marshall, 1993).

### Turkish history

In Turkish history, two names are noteworthy. The first, Mahmud al-Kashgari (1008-1105) devoted himself to Turkic languages. After studying all the classical sciences of the period, he crossed the whole of Central Asia heading to Anatolia, and then to Baghdad where he settled in 1043. He travelled throughout all the cities, plains, mountains and deserts inhabited by Turkic people, and explored their language and customs for 15 years. He completed the first comprehensive dictionary of Turkic languages *the Dīwānūl-Luġat al-Turk* in 1074, the original copy of which is now preserved in the National Library in Fatih, Istanbul (Yildiz, 2009).

The other, Yusuf Has Hacıp (1017-77) was an 11<sup>th</sup> century Uyghur scribe from the city of Balasaghun, the capital of the Karakhanid Empire, who completed the first literary work in Turkish history. He wrote his political essay, the 'Kutadgu Bilig' (Knowledge that brings happiness) in the masnavi form in 1070, and dedicated it to Ulu Bughra Khan, ruler of the Karakhanids and was awarded the title Ulu Khass Hajib (an honorar position similar to 'Privy chamberlain'). Both masterpieces provide information on the history, folklore, languages and cuisine of Turkic societies over a very wide geographical area, and note that Turks used yoghurt to have a healthy diet and to prevent or treat gastrointestinal problems (Atalay, 2006; Dankoff, 1983). Yoghurt is a Turkish word deriving from the verb 'yoġuşmak' meaning to thicken or curdle.

## 5. Modern history

Many major events brought dramatic changes to the world around the late 15<sup>th</sup> century (Dunan, 1964). The invention of the printing press was a great landmark for mankind and can be said to be the start of the modern era of history.

### Ottoman history

An amazing story about yoghurt from the 16<sup>th</sup> century is that the French King, Francis I, suffered from a severe gastrointestinal disease that famous physicians had failed to cure and his mother, therefore, reluctantly asked Suleiman the Magnificent to send a doctor for his treatment. Suleiman the Magnificent sent a Jewish doctor with goats to Paris by ship. The Jewish Ottoman doctor first prepared yoghurt by milking his goats and then added some unknown substances into the yoghurt in strict secrecy, according to a miraculous formula (Wikipedia, 2014a). This special yoghurt formula was called 'the milk of eternal life' by Francis I, who brought about many radical modernisations in France:

- French became the official language replacing Latin;
- 'Collège de France', one of the first French universities, for the study of social sciences was founded;
- it was the era of the Renaissance in France (Andrea del Sarto, Leonardo Da Vinci).

### Academic history

Arnaldus de Villa Nova, a Catalan physician and scientist working on physics, chemistry, astrology and medicine during the 14<sup>th</sup> century produced the mass circulation book on the subject of wine, entitled 'Liber de Vinis', which was also the first academic source on the medicinal use of wine. Villa Nova recommended using wine as a treatment for various illnesses, such as dementia and sinus disorders (Johnson, 1989). The first paper on wine in a scientific journal is a report on the combination of wine and medicines for the treatment of rickets and dysentery published in 1790 under the title 'Journal of a voyage to New South Wales' (White, 1962).

### Microbiological history

The light microscope was first designed by Anton van Leeuwenhoek, then improved by Robert Hook. They opened the doorways to the microscopic universe and were the first to discover bacteria, yeast and blood elements. The discovery of the microscopic universe dramatically changed the course of human history (Egerton, 2006).

### Pasteur institute

It was Pasteur and his successors who had the most significant impact on microbiology. The idea of using beneficial bacteria became popular in parallel to the

advances in microbiology, particularly in the Pasteur institute. Lactic acid producing bacteria were first discovered by Pasteur in 1857. Then in 1878, Lister reported the isolation of these bacteria from rancid milk. Scientists at the same institute also isolated lactic acid bacteria from the intestinal tract between 1880 and 1888 (Neubauer and Mollet, 2002).

Henry Tissier, a pediatrician of the Pasteur Institute discovered *Bifidobacterium* spp. in 1889. Tissier noted that bifidobacteria are the dominant microorganism in the gut flora of breast-fed infants, and named the bacteria as *Bacillus bifidus communis*. He reported his finding in his dissertation thesis in Paris University, named '*Recherches sur la flore intestinale des nourissons (et at normal et pathologique); 1900*'. He also reported that acute gastroenteritis could be cured if the imbalance in favour of harmful bacteria causing the disease could be normalised by bifidobacteria (Hughes and Hoover, 1991). Although not fully credited in literature, Henry Tissier was the first scientist to address the idea that friendly bacteria could be used in the treatment of intestinal diseases, and that article was presented in 1906 at the University of Paris (Tissier, 1906).

However, in the majority of scientific papers, Elie Metchnikov has always been regarded as the father of the idea that probiotics are beneficial to human health. His reputation is related more to his book 'The prolongation of life; optimistic studies' published in 1908 than to having been awarded a Nobel Prize for his work on phagocytosis in the same year (Tan and Dee, 2009). In this book, he suggested that phagocytosis in intestinal flora produces toxic substances, leading to the ageing process, and if these proteolytic microbes could be prevented through the work of future studies, the result would be longer life expectancy (Schmalstieg and Goldman, 2008).

Metchnikov suggested that lactic acid bacteria in dairy products could lower the pH in the colon by breaking down lactose and inhibiting the growth of proteolytic bacteria. The evidence for this hypothesis was the fact that the villagers in a mountainous area of Bulgaria who consumed a large amount of fermented milk products lived longer than the general population. Metchnikov directed his studies in support of this thesis and also announced that he drank sour milk everyday to remain healthy. However, this idea had been suggested to him from a meeting with a young Bulgarian physician, Stamen Grigorov, who had made this discovery concerning Bulgarian yoghurt in 1905.

### Bulgarian physician Stamen Grigorov: the untold story

Although Elie Metchnikov is almost always credited with the idea of the beneficial effects of foods containing friendly bacteria, there is another hero in the background;

a Bulgarian physician, Stamen Grigorov (1878-1945). He was working as the chief assistant in the microbiology laboratory of Professor Léon Massol in Geneva University when he identified a species of *Lactobacillus* in the starter culture of a fermented Bulgarian dairy product. His paper was published in the prestigious French scientific journal; *Étude sur une lait fermenté comestible. Le 'Kisselo mléko' de Bulgarie. Revue Médicale de la Suisse Romande; 1905:10*, giving full information about the agent, a lactic acid bacillus, in the Bulgarian yoghurt, kisselo mliako.

Prof. Massol wrote a letter to Elie Metchnikov stating 'He is a rare person and I think he could be very useful for you indeed. After numerous and consistent experiments in my laboratory he succeeded in finding and isolating the fermenting agent in Bulgarian kisselo mliako whose ferment/starter had come from Bulgaria. You work driven by the ambition to find means to prolong human life. Further to your remarkable phagocytes, please think now about the Bulgarian kisselo mliako and about this rodshaped bacillus found by Grigorov which I have also seen under the microscope. Probably, he will be useful for you' (Stamen Grigorov Foundation, 2014).

Metchnikov immediately responded to invite Grigorov, who then visited the Pasteur institute to present his study accompanied by yoghurt and a microscope in the great hall when he was only 27 years old. He presented an unexpectedly successful demonstration in the Pasteur Institute Great Hall, Stamen Grigorov thanked the institute for the opportunity to present the results from his investigations to so demanding an audience and finally proposed that yoghurt might be the reason why people from his region lived so long.

The Pasteur Institute offered him work in Paris or in Sao Paolo, running a new office of the Institute. However, he refused the offers stating that he had promised to return to Trun, Bulgaria, to serve his people (Stamen Grigorov Foundation, 2014). The Pasteur institute later commissioned Metchnikov to focus on this subject, which is why this bacteria was named *Lactobacillus bulgaricum* by Metchnikov's assistants Coendi and Mikelson in recognition of Grigorov. However, almost all the available medical sources declare the reason for the naming of this species as Metchnikov's statement that 'Bulgarians live longer'.

### German physician Alfred Nissle

Before the discovery of antibiotics, a German Professor, Alfred Nissle isolated a non-pathogenic strain of *Escherichia coli* from the faeces of two soldiers not affected by the outbreak of dysentery (shigellosis) on the Dobruca Front during World War I. Studying this strain, he inhibited colonisation of the pathogen bacteria, resulting in the discovery of *E. coli* Nissle strain 1917, which has been

frequently used since in both medical and food sectors. This non-pathogenic bacterium inhibits the adherence of pathogenic bacteria with the secretion of certain bacteriocins, and replaces intestinal pathogens. The results of studies on this strain have revealed that probiotics can also be used in other diseases of the gastrointestinal tract, not only in infectious diseases (Sonnenborn and Schulze, 2009).

### The rise of yoghurt

During the time of Balkan unrest at the beginning of the 20<sup>th</sup> century, Emmanuel Karasu from Thessaloniki, an Ottoman senator and member of the Young Turks movement, decided to send his nephew back to their land of origin. Thus, the nephew, Isaac Carosso, a physician, moved to Barcelona (Wikipedia, 2014b). He noticed that many of his patients had gastrointestinal complaints and he recommended yoghurt for better intestinal health. He started to produce yoghurt by conventional methods with the pure bacterial cultures he obtained from the Pasteur institute or occasionally from Thessaloniki. After World War I, he opened a small shop to produce and sell yoghurt himself. He named the shop after his new son 'Danino' (meaning Little Daniel) (Fuller, 1995). Isaac then moved to France in 1929, which was a better place for marketing, but with the outbreak of World War II, he left Paris for the USA, where he founded the first American yoghurt factory in 1942, 'Dannon Milk Products'.

Two Armenians, Sarkis and Rose Colombosian who emigrated to the USA after World War I, started to sell their home-produced yoghurt from a horse-drawn cart, with the name 'madzoon' which means yoghurt in Armenian. Sales were not good as it was an unfamiliar name, so they began to sell the product as yoghurt since Turkish was then a lingua franca among the main consumers of yoghurt and similar products (Massachusetts Historical Society, 2014). Starting from a small kitchen in Andover, MA, USA, they founded the company 'Colombo and Sons Creamery' in 1929, which was the first yoghurt brand in the USA. The introduction in 1929 gave Americans their first taste of yoghurt and 80 years later, popularity continues to grow. After increasing sales, they developed their own brand, 'Colombo Yoghurt' which was then sold to General Mills in 1993.

Meanwhile in the Far East, Dr. Minoru Shirota obtained the first culture of *Lactobacillus casei* strain *Shirota* isolated from the human intestine in the Microbiology Laboratory of the Faculty of Medicine at Kyoto University, Japan in 1930. Several studies have demonstrated that the strain discovered by Shirota is resistant to gastric acid and bile acid, and can therefore reach the lower intestine after oral administration. In 1935, Dr. Shirota developed 'Yakult', a dairy product manufactured with this probiotic bacteria, and introduced it to the market. The name 'Yakult' was derived from the word 'yoghurt' in Esperanto, the proposed universal language of

**Table 1. Summarized history of medicine.**

2000 BC	Polytheistic religions era	Take this herb and eat, it's good for you
1000 AD	Monotheistic religions era	That herb is bad, you'd better say this pray
1500 AD	Renaissance development era	That pray is a superstition, you'd better drink this elixir
1800 AD	Industrial revolution era	What's the use of that elixir, you'd better take this pill
1950 AD	Pharmaceutical revolution era	That pill is ineffective, you'd better take this antibiotic
2000 AD	Electronic media era	That antibiotic is chemical, you'd better eat this herb
2010 AD	Evidence-based medicine era	No study on that herb, you'd better take this probiotic

the 1880s (Yakult, 2014). He hypothesised that the daily intake of this fermented product might promote intestinal health, and prolong the lifespan.

### The era of probiotics

Finally, comes the 'Era of probiotics' which can be easily accessed on many sources with almost similar information. That's why, we want to end up with summarising the history of medicine (Table 1).

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