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Control of Gastroenteritis: The Probiotic Therapy Alternative in Nigeria

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ABSTRACT

Microorganisms have been implicated as the major etiological agents of gastroenteritis. Some of these agents include *Shigella*, *Salmonella*, *C. difficile*, rotaviruses and enterotoxigenic *E. coli*. The prevention and treatment of gastroenteritis has been by the use of antibiotics. However, antibiotic therapy has been found to have some disadvantages, such as the development of resistant microbial strains after oral treatment, disruption of the gut microbial balance, and elimination of the beneficial microbial population in the gut and intestinal upset. Recently, probiotics have been found to be a suitable alternative to the use of antibiotics in the prevention and treatment of a diverse spectrum of gastrointestinal disorders such as infectious bacterial and viral diarrhoea, small bowel bacterial overgrowth, and inflammatory bowel disease. The use of probiotics in treating and preventing microbial gastroenteritis has the following advantages: a relatively low cost, unlikelihood to increase the incidence of antibiotic resistance strain that is common when antibiotics are applied, and multiple mechanisms of inhibiting intestinal pathogens. Application of probiotics will certainly be an effective means of controlling diarrhoea and fever associated with gastroenteritis that is common in Africa.

Keywords: gastroenteritis, probiotics, therapy
Abbreviations: AIDS, acquired immune deficiency syndrome; ***E. coli***, *Escherichia coli*; **ETEC**, enterotoxigenic *E. coli*; **GG**, Gorbach and Goldin; **GIT**, gastrointestinal tract; **HIV**, human immunodifficiency virus

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INTRODUCTION

Gastroenteritis is the irritation and inflammation of the digestive tract. This condition may cause abdominal pain, vomiting and diarrhoea. The major etiological agents implicated in gastroenteritis are bacterial and viral entities. The major antidote for the treatment and prevention of gastroenteritis has been the use of antibiotics. However, despite numerous therapeutic improvements, especially in the field of antibiotics, gastrointestinal infections and their consequences remain a major clinical problem (Rolfe 2000). This is because the use of antibiotics had been found to result in the development of resistant microbial pathogens, intestinal upsets after oral treatment, elimination of beneficial microbial population in the gut, and delay in further recolonisation by normal colonic flora (Fuller 1989; Rolfe 2000).

The side effects associated with the use of antibiotics in the treatment of gastroenteritis definitely necessitated the search for a suitable and friendlier alternative. Probiotics are an attractive treatment alternative to antibiotics. This paper therefore focuses on the potentials of probiotics in the prevention and treatment of microbial gastroenteritis in animals and humans.

IMPORTANCE OF THE GUT FLORA

The gastrointestinal tract (GIT) of man and animals consists of several different anatomically distinct regions. Each region is colonised by characteristic, principally prokaryotic microbiota, the composition of which varies from site to site

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in different animal species and which may be influenced by factors such as age of the individual and diet (Linton and Dick 1990). Within each region there are several habitats including the mucosal surface, crypts, and the lumen; each is colonised by different bacterial communities. The bacteria commonly found in the intestinal flora are *Lactobacilli*, *Bifidobacterium*, *Coliforms*, *Enterococci* and *Staphyloccoci*. In breast fed infants anaerobic bacilli of the *Bifidobacterium* group predomi-nates (Cruickshank 1952). In adults, the microbiota, particularly of the large intestine is relatively stable, at least in terms of the principal genera, and normally appears to remain so in spite of considerable changes in the circumstances of the individual. This climax microbiota is relatively stable and makes it relatively difficult for pathogens to gain a foothold and multiply to cause disease. van der Waaij (1983) described this as colonisation resistance. The gut flora may also be manipulated to prevent infection through competitive exclusion (Pivnick and Nurmi 1982). Competitive exclusion involves principally the administration of adult caecal microbiota to young chicks so as to prevent colonisation of their intestine with Samonellae, which may be present in either their environment or their feed.

The ability of the normal gut flora to create a balance, which will ensure that pathogens do not multiply, will be disturbed under certain circumstances. Antibiotic therapy is a good example, which dramatically modifies the intestinal flora and lowers colonisation resistance, and in such circumstances potential pathogens such as *Salmonella* and *C. difficile* may multiply and cause clinical illness in the host. Moreover, reduced production of acid by the stomach and conditions which induce small bowel stasis may cause a predisposition to multiplication of "non-pathogenic" organisms in the small intestine (Linton and Dick 1990). To maintain an intestinal microbial balance, the administration of probiotics has been found to be effective (Loizeau 1993; Parkhurst 1999).

WHAT ARE PROBIOTICS?

Microorganisms have been essential to food and alcohol fermentation for thousands of years. Over the last century, different microorganisms have been used for their supposed ability to prevent and cure diseases, leading to the coining of the term probiotics, or 'pro-life' (Lilly and Stillwell 1965).

There have been several definitions to the word probiotics over the years. Lilly and Stillwell in 1965 used it to describe substances produced by one protozoan which stimulates another, but Parker in 1974 described it as animal feed supplements which had a beneficial effect on the host animal by affecting its gut flora. Parker's definition clearly mentions organisms and substances which contribute to the intestinal microbial balance. Fuller (1989) argued that the latter definition is too imprecise, since substances mentioned would include antibiotics. He later revised the definition as 'A live microbial feed supplement, which beneficially affects the host animal by improving its intestinal microbial balance'. This new definition emphasises the importance of live cells as an essential component of an effective probiotic and removes the confusion created by the use of the word substances. Other workers had also given their own definition of the term probiotic. For instance, Donohue *et al.* (1998) described probiotic bacteria as viable bacteria when applied in single or mixed culture, and exhibit a beneficial effect on the health of the host. This definition encompasses the application of either axenic or mixed cultures in the treatment of disease.

The most recent definition was by Schrezenmeir and de Vrese (2001). They defined probiotics as viable microbial food supplements which beneficially influence the health of the host. This new definition clearly points out the health promoting effect of probiotic agents.

The concept of probiotics evolved around 1900. At this time Henry Tissier, a French Paediatrician, observed that children with diarrhoea had in their stools a low number of bacteria characterised by a peculiar, Y-shaped morphology. These "bifid" bacteria were, on the contrary, abundant in healthy children (Tissier 1906). Nobel price-winning Elie Metchnikoff in 1907 advocated that the consumption of lactobacilli helps in controlling endogenous intoxication (autointoxication) caused by wrong types of components in the intestinal flora. He pointed out that the long, healthy lives of Bulgarian peasants were the result of their consumption of fermented milk products. The works of Metchnikoff and Tissier were the first to make scientific suggestions about the probiotic use of bacteria. The first clinical trials were done in the 1930's on the effect of probiotics on constipation (Koop-Hoolihan 2001).

A lot of research on probiotics were carried out after that time and have increased steadily since then, but much of it is in Europe, Asia, and America. Presently, probiotics are available in a variety of food products and supplements. In the USA, the food products containing probiotics are almost exclusively dairy products, fluid milk, and yoghurt, due to the historical association of lactic acid bacteria with fermented milk (Koop-Hoolihan 2001). The most frequently used bacteria in these products belong to the genera: *Lactobacillus*, *Bifidobacterium*, and *Streptococcus*.

CHARACTERISTICS OF A GOOD PROBIOTIC

It is quite possible to get a positive result experimentally when a probiotic is applied, often; field trials results are variable in some cases (Fuller 1989). This author reasoned that the result is bound to be variable because it operates by reversing stress factors, which may or may not be present. This is particularly likely in the case for stimulation when the organism responsible for the growth depression is not always present in the gut. Variation has also been observed when antibiotics and other chemical growth promoters are applied.

The problem with some commercial preparations is poor quality control. Clements *et al*. (1983) found that two batches of the same product gave different results when used to treat induced *E. coli* diarrhoea in human adults. It has also been observed that some preparations claiming to have viable cells present in large numbers have only very low numbers and others which claim to have one species of microorganism have a totally different species (Fowler 1969; Gilliland 1981).

Fuller (1989) listed the following as features of a good probiotic:

(i) It should be a strain, which is capable of exerting a beneficial effect on the host animal, e.g. increased growth or resistance to disease;
(ii) It should be non-pathogenic and non-toxic;
(iii) It should be present as viable cells, preferably in large numbers;
(iv) It should be capable of surviving and metabolising in the gut environment e.g., resistant to low pH and organic acids;
(v) It should be stable and capable of remaining viable for periods under storage and field conditions.

COMPOSITION OF PROBIOTICS

Probitics can be compounded in various ways depending on the sort of use intended. They can either be included in the pelleted feed or produced in the form of capsules, paste, powder or granules which can be used for dosing animals directly or through their food (Fuller 1989). Probiotic preparations may be made up of a single strain or may contain any number up to eight strains. The advantage of multiple strain preparations is that they are active against a wide range of conditions and in a wider range of animal species.

Fuller (1989) listed the following organisms as species used in probiotic preparation: *Lactobacillus bulgaricus*, *L. plantarum*, *Streptococcus thermophillus*, *Enterococcus faecium*, *E. faecalis*, *Bifidobacterium* spp., and *Escherichia*

coli. Apart from *L. bulgaricus* and *Strep. thermophilus*, all the other organisms are all intestinal strains.

Lactobacilli, Streptococci and Bifidobacteria are the commonly used groups in the production of probiotics. The justification for the use of Lactobacilli stems from studies which show that when the gut flora develops after birth, as Lactobacilli increases, other components of the flora decrease (Smith 1965). Fuller (1978) had also reported that lactobacilli exert a controlling effect on *Escherichia coli* in gnotobiotic chicks.

MODE OF ACTION OF PROBIOTICS

The mechanisms by which probiotics exert their effects on the host are still speculative (Koop-Hoolihan 2001). Their beneficial effects may be mediated by direct antagonistic effect against specific groups of organisms, resulting in a decrease in numbers or by an effect on their metabolism or by stimulation of immunity. Probiotics antagonise pathogens through production of antimicrobial and antibacterial compounds such as cytokines and butyric acid (de Vuyst and Vandamme 1994; Dodd and Gasson 1994; Kailasapathy and Chin 2000); reduce gut pH by stimulating the lactic acid producing microflora (Langhendries *et al*. 1995); compete for binding and receptor sites that pathogens occupy (Fujiwara *et al*. 1997; Kailasapathy and Chin 2000); improve immune function and stimulate immunomodulatory cells (Isolauri 1995; Rolfe 2000); compete with pathogens for available nutrients and other growth factors (Rolfe 2000); or produce lactase which aids in lactose digestion.

EXPERIMENTAL AND CLINICAL STUDIES IN THE PREVENTION AND TREATMENT OF GASTROENTERITIS USING PROBIOTICS

There are many microbial etiological agents that are responsible for gastroenteritis. Some well known examples of these are *Shigella*, *Salmonella*, *C. difficile*, Rotaviruses, and enterotoxigenic *E. coli.* Probiotics have been studied in the treatment and prevention of microbial gastroenteritis. Some documented gastroenteritis cases treated with probiotics are presented below.

Closridium difficile-associated intestinal disease

C. difficile is a classic example of the opportunistic proliferation of an intestinal pathogen after breakdown of colonisation resistance due to antibiotic administration. *C. difficile* is known to colonise the intestine and releases two protein exotoxins, toxin A and B, which mediate the diarrhoea and colitis caused by this microbe (Rolfe 2000). There have been cases of relapsing in *C. difficile* infection, once treated with vancomycin and metronidazole is discontinued (Fekety *et al*. 1989; Young *et al*. 1995). The mechanism of relapse is unknown but is probably due to the survival of *C. difficile* spores in the intestinal tract until the antibiotic is discontinued (Walters *et al*. 1983). The spores then germinate and produce the toxin. *Saccharomyces boulardii* has demonstrated the most promise for use in *C. difficile*-associated intestinal disease (Mcfarland *et al*. 1994). In a placebo-controlled study, they examined standard antibiotic therapy (metronidazole or vancomycin) with concurrent *S. boulardii* or placebo in 24 adult patients, 64 patients with an initial episode of *C. difficile* disease and 60 patients with history of at least one prior episode of *C. difficile* disease, *S. boulardii* significantly inhibited further recurrences of disease.

Probiotic treatment of traveller's diarrhoea

Various infectious agents can cause traveller's diarrhoea however, enterotoxigenic *E. coli* (ETEC) is the most common. An attack of ETEC can interrupt a holiday; hence a safe, inexpensive, and effective drug against traveller's diarrhoea would have important public health implications (Rolfe 2000). Several probiotics examined for ability to prevent traveller's diarrhoea, and these include *Lactobacillus*, *Bifidobacterium*, *Streptococcus* and *Saccharomyces* (Oksanen *et al*. 1990; Scarpignato and Rampal 1995; Hilton *et al*. 1997). In a study of Finnish travellers to Turkey, the travellers had two destinations (Oksanen *et al*. 1990). In one destination, *Lactobacillus* GG provided pro-tection against traveller's diarrhoea but failed to protect travellers at the other destination. Different etiologic agents may have been involved in these two locations (Rolfe 2000). In another study, probiotic lactobacilli isolated from faeces of human neonate and fermenting corn slurry was found to prevent infectious diarrhoea in rats experimentally infected with enterotoxigenic *E. coli* and *Shigella dysenteriae* respectively (Oyetayo and Osho 2004; Igabasan *et al*. 2005).

Probiotic treatment of rotavirus diarrhoea

Rotavirus infection causes gastroenteritis, characterised by acute diarrhoea and vomiting. This is a significant cause of infant morbidity and mortality, particularly in developing countries (Majamaa *et al*. 1995; Reid *et al*. 2003). *Lactobacillus* has demonstrated some promise as a treatment for rotavirus infection (Isolauri *et al*. 1994; Majamaa *et al*. 1995). In a study, 74 children (ages 4-45 months) with diarrhoea were treated with either *Lactobacillus* GG or placebo (Isolauri *et al*. 1995). Approximately 80% of the children with diarrhoea were positive for rotavirus. The investigation demonstrated that the duration of diarrhoea was significantly shortened (from 2.4 to 1.4 day) in patients receiving *Lactobacillus* GG.

Helicobacter pylori gastroenteritis

H. pylorus has recently been shown to be an important etiologic agent of chronic gastritis as well as gastric and duodenal ulcers. *Lactobacillus species* has been shown to be antagonistic to *H. pylori* both *in vitro* and *in vivo* in a gnotobiotic murine model (Kabir *et al*. 1997; Aiba *et al*. 1998). Clinical studies have been performed in humans with conflicting results, some showing modest protection, and others showing no protection (Rolfe 2000).

HIV/AIDS diarrhoea

Diarrhoea is a very serious consequence of human immunodeficiency virus (HIV) infection. *Saccharomyces boulardii* was used to treat 33 HIV patients with chronic diarrhoea (Born *et al*. 1993). In these double blind studies, 56% of patients receiving *S. boulardii* had resolution of diarrhoea compared with only 9% patients receiving a placebo. In another study on the efficacy and safety of *Lactobacillus rhamnosus* GG (LGG) on prolonged, non-infectious diarrhoea in HIV patients on antiretroviral therapy, Salminen *et al*. (2004) observed that probiotic LGG was well-tolerated in HIV infected patients. The authors also reported that there were no significant differences in non-infectious diarrhoea or gastrointestinal symptoms compared to placebo in a crossover study. It has been reported that diarrhoea and other gastrointestinal (GI) symptoms in HIV patients arise from multiple causes, but are often a direct side effect of highly active antiretroviral therapy (HAART) (Bardsley-Elliot and Ploske 2000; Cvetkovic and Goa 2003). Antiretroviral drugs such as nelfinavir, lopnavir, rotinavir are known to induce diarrhoea in HIV patients. The benefits of supplementing the diet with probiotics, soluble fibre, and/or glutamine had been reported for patients suffering from diarrhoea induced by various clinical conditions including HIV infection (Savarese *et al*. 2001; Ziegler 2001). In a pilot study using probiotics, soluble fibre, and L-glutamine (GLN), Heiser *et al*. (2004) observed the benefit of the above dietary interventions in treating antiretroviral drug-related diarrhoea in HIV patients.

Inflammatory bowel diseases

Inflammatory bowel diseases such as Chron's disease and ulcerative colitis/ponchitis are chronic and painful. Bacteria overgrow in the pouch, resulting in degradation of the mucus overlaying the epithelial cells (Madden *et al*. 1990). Mixtures of concentrated probiotics have been shown to decrease the number of patients relapsing with pouchitis compared to placebo over 12- and 18-month periods (Giochetti *et al*. 2000).

STATUS OF PROBIOTICS IN NIGERIA

There is dearth of information about the clinical application of probiotics in Nigeria. In a survey on the receptivity of probiotic products among premenopausal female students in an African University, Anukam *et al*. (2004) reported that female students in Nigeria are willing to accept probiotic products. The authors however stated that there is a dearth of information with regards to knowledge, availability, and receptivity for probiotic products especially in sub-Saharan African Countries. Major reports on the importance of probiotics have been mainly experimental results conducted using animal models (Anukam *et al*. 2004; Oyetayo 2004; Oyetayo and Osho 2004). In one of such experimental study, Oyetayo (2004) observed that rats orogastrically dosed with *Lactobacillus* sp. and simultaneously infected with enterotoxigenic *E. coli* did not show signs of diarrhoeic faeces which was evident in the control that was experimentally infected with enterotoxigenic *E. coli* alone (**Table 1**).

Table 1 Faecal characteristics of rats orogastrically dosed with *Lactobacillus species* and experimentally infected with entorotoxigenic *E. coli*.

Isolates/Designation	Colour of Faeces	Texture of Faeces	Remark
Lactobacillus acidophilus (H)	Light brown	Soft and moist	No sign of diarrhoea
Lactobacillus plantarum (S)	Light brown	Soft and moist	No sign of diarrhoea
Control*	Light brown	Wet and loose	Diarrhoeic faeces

* Rats were challenged with *E. coli* alone.

In Africa, one of the major challenges is the threat of diseases associated with unhygienic condition. One of these diseases is gastroenteritis caused by microbial agents (viruses and bacteria). Probiotics have been found to be able to effectively wade off the causative agents of these infectious diseases by producing metabolites that are active against them. This can bring about a reduction in the incidences of diarrhoea and fever associated with gastroenteritis. Therefore, efforts should be geared towards isolation, characterisation, and clinical application of probiotics in Nigeria.

FUTURE PERSPECTIVES

The application of probiotics in the treatment and prevention of gastroenteritis has been well established. Hence, there should be a more concerted effort toward the exploitation of biotherapeutic potentials of probiotics isolated locally. Any isolate that possess potential probiotic characteristics must be subjected to rigorous scientific studies that are required of chemical drug entities, including randomized, placebo-controlled, double blind studies, pharmacokinetics studies and multicenter trials to establish reproducibility (Rolfe 2000).

There are many potential advantages to probiotics over conventional therapy and these include relatively low cost, the fact that probiotics are unlikely to increase the incidence of antibiotic resistance, and the multiple mechanisms by which probiotics presumably inhibit pathogens, thereby decreasing the chances for development of resistance against the probiotics (Rolfe 2000).

The application of genetic engineering to enhance the activity of probiotics should be explored. This should lead to the development of probiotic strains, which can survive in the intestinal tract and with ability to produce metabolites that will make them more efficacious as boitherapeutic agents.

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