

PREBIOTIC AND PROBIOTIC TREATMENT TO REDUCE ORAL DYSBIOSIS AND PREVENT OR TREAT PERIODONTITIS, HALITOSIS AND DENTAL CARIES

DESCRIPTION OF THE TECHNOLOGY

In the Spanish population, >25% adults have periodontitis and/or halitosis, ~50% children have cavities, and cardiovascular diseases are the 2nd cause of death. The research developed shows that these diseases have a possible common treatment focused on the oral microbiota.

Certain oral bacteria convert nitrate to nitrite and nitric oxide (a vasodilator), which lowers blood pressure and has antidiabetic effects. The research group has found that this bacterial function also prevents the 3 main oral diseases (caries, periodontitis and halitosis). A diagnostic test has been developed to determine if a person has these bacteria. It has been shown that this process of nitrate transformation can be increased with new prebiotics and probiotics developed by our group. A prebiotic is a substance that when administered in the diet promotes the growth of beneficial bacteria present in the body; a probiotic is a microorganism that when administered in appropriate doses, performs this beneficial function directly. This is the first time that a beneficial treatment for all these diseases has been described simultaneously.

A composition comprising nitrate (from fruits or vegetables, as well as from nitrate salts) is provided for use in reducing or preventing oral dysbiosis and/or increasing oral eubiosis, i.e. a change in the bacterial composition and functions of oral biofilms in humans and domestic animals, by decreasing the amount of bacteria associated with disease and increasing the amount of bacteria associated with health. This provides an acute treatment

or prevention with immediate effects that last several hours after ingestion or application, effective against the three main oral diseases mediated by biofilms (caries, periodontal diseases - gingivitis, periodontitis or periimplantitis - and halitosis). The prebiotic can be administered topically (e.g. toothpaste or dental varnish), as a food supplement (e.g. ingested preparations), or in tablet form, among others. Our prediction is that this patent will be the origin of a whole range of new oral health products and that will pave the way for the development of prebiotics as natural active ingredients, which would be complementary to fluoride and an alternative to oral antiseptics. Another protected product is the anti-halitosis tablet that would reduce the production of volatile gases that cause bad breath for 6 hours.

The composition may also include beneficial bacterial strains, which the research group have developed as probiotics. This may be useful in individuals in the absence of these nitrate-reducing organisms for whom the supply of the prebiotic is not sufficient. Therefore, the diagnostic test uses a saliva sample to determine whether the person has a high, medium or low nitrate-reducing capacity. In this last case, it is advisable to supply the prebiotic together with the probiotic, in order to increase the nitrate reduction capacity. This test therefore allows a personalized treatment according to the individual needs of the patients. These patients can be for oral health reasons or for systemic health reasons, for example diabetes, cancer or cardiovascular risk.

MARKET APPLICATION SECTORS

Pharmaceutical sector, oral hygiene sector, nutritional supplements sector and clinical diagnosis sector.

TECHNICAL ADVANTAGES AND BUSINESS BENEFITS

There are oral health products on the market that use arginine as a prebiotic, favoring bacteria that use arginine to neutralize acids. It is therefore a prebiotic suitable for preventing caries, but not halitosis or periodontitis. Therefore, our nitrate-based products have multiple applications. Moreover, as our technology protects the use of nitrate-rich plant extracts, it will increase social acceptance (products of natural origin) and facilitate regulatory aspects.

Some of the protected products also represent a revolution in the field of oral health, as would be the case with the anti-caries pill. This would be a disruptive strategy consisting of an ingested tablet that for at least 6 hours maintains the acid neutralizing capacity of saliva, due to the natural recycling of nitrate by the salivary glands.

Another advantage of the product is that in addition to improving oral health, it would have a direct effect on improving cardiovascular health, through the production of nitrite, which can serve as a reservoir for the availability of vasodilatory agents. Finally, the presence of nitrate-reducing organisms and the salivary recycling mechanism of nitrate make possible the development of supplements and products for oral health in domestic animals.

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CURRENT STATE OF DEVELOPMENT

The necessary dose of the prebiotic has been determined to carry out its function. Validation tests have been done on an *in vitro* oral biofilm model, showing benefits against caries, periodontitis and halitosis (published in Rosier et al. Sci. Reports 2020). It has been shown that taking the nitrate supplement (prebiotic) is effective in humans to prevent caries, by neutralizing salivary acids. The best probiotics have been isolated and selected, genetically characterized and tested *in vitro* in an oral biofilm model (published in Rosier et al. Frontiers Microbiol 2020). The absence of mobile elements, antibiotic resistance and virulence genes in the genomes of the patented probiotics has been established. *In vitro* oral biofilm tests have been conducted to test the efficacy of prebiotics and probiotics against periodontitis. Two types of diagnostic tests have been developed to establish the ability to reduce salivary nitrate.

INTELLECTUAL PROPERTY RIGHTS

Technology protected by European patent (priority year 2019); ownership of the result, Fundación FISABIO.

COLLABORATION SOUGHT

Licensing or co-development agreements for the development and commercialization of the diagnostic kit as well as the oral hygiene products associated with the prebiotic and probiotics. Clinical trials are planned or underway to test the efficacy of the prebiotic against periodontitis and halitosis *in vivo*.

RELATED IMAGES

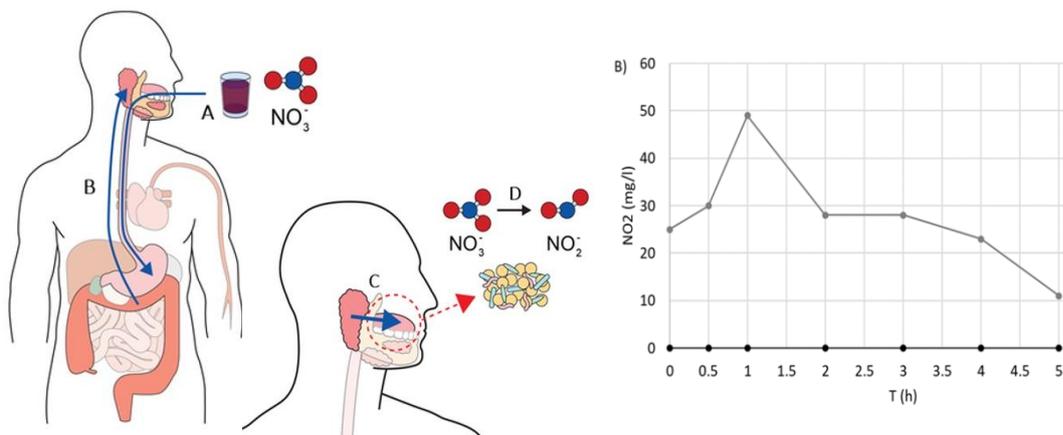


Figura 1. Reducción de nitrato a nitrito por las bacterias orales tras la ingestión del prebiótico. Cuando consumimos alimentos con nitrato, como zumo de remolacha, el compuesto llega a nuestro intestino (A), pasa a la sangre y retorna a las glándulas salivales (B). Estas glándulas concentran el nitrato en la saliva hasta 10 veces más que la concentración en el plasma sanguíneo (C). Así, nuestras glándulas salivales suministran el nitrato de la dieta a las bacterias orales para que lo reduzcan a nitrito (D), una función que no puede ser realizada por el cuerpo humano. La gráfica de la derecha muestra los niveles salivales de nitrito en un individuo con y otro sin las bacterias reductoras.

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