First Multiplatform Application for Pharmacies in Spain, Which Guides the Prescription of Probiotics according to Pathology

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Featured Application: The tool developed provides a quick consultation of which probiotics are suitable for a pathology.

Abstract: The study of the intestinal microbiota is one of the biggest challenges in the current clinical environment. In this context, probiotics have been a focus of interest to achieve the stability of the intestinal microbiota, due to probiotics’ key role in its regulation. The development of an automated system that allows practitioners to easily search for the optimal probiotic is the main objective of this study. Although it is true that there have been previous attempts of applications with this purpose, only authorized probiotics available in the countries of origin, Canada and the USA, were included. This event was a limitation when looking for those endorsed in other countries such as Spain. Thus, a system has been developed from free and multiplatform technologies that allow its use without any cost, finding, in a simple way, those probiotics that would be ideal for each pathology, either from a browser or from a cell phone.

Keywords: probiotic; microbiota; software; multiplatform app

1. Introduction

The human microbiota is the population of all microorganisms (bacteria, fungi, archaea and viruses) with their genes and metabolites that colonize the body, including the skin, the oral cavity and the gastrointestinal, genitourinary and respiratory tracts. The highest concentration of microbes is found in the intestine and is called intestinal microbiota [1].

The microbiota has a very high real impact on human health, and understanding its impact is one of the most important challenges facing clinical care today [2]. In fact, the need to establish homeostatic relationships with the microbiota has been proposed as one of the main enhancers of the mammalian immune system. In this way, host tissues have evolved, together with the microbial ensemble they contain [3].

The intestinal microbiota provides the human body with nutritional, metabolic and protective effects for the development and maintenance of the digestive system itself. With most avant-garde techniques, it has been discovered that a relevant amount of bacteria are not cultivable, and knowledge has been obtained about the relationship between diverse microorganisms that inhabit the body. The intake of the proper amount of the right microorganisms can help regenerate the composition and concentration of the microbiota, thus eliminating problems such as dysbiosis [4].

If one suffers from a pathology or takes antibiotics, the intestinal microbiota can become unbalanced, which can make the human body more vulnerable to certain infections. For certain pathologies, it is advisable to prescribe probiotics, as they can help rebuild the microbiota and position it where the disease, or even antibiotics, has broken the balance, so that the use of probiotics is an increasingly used alternative to balance and restore...
the microbiota [5,6]. This process is illustrated in Figure 1, in which it can be seen how an imbalance in the microbiota phyla can lead to imbalance and this can be repaired by dispensing the correct probiotic.

![Gut Microbiota](image)

**Figure 1.** Process of imbalance in the intestinal microbiota and its recovery through the use of probiotics. The logo of the application (Probiotic) designed in this study is illustrated, whose purpose is to collaborate with the dispensing of the correct probiotic to achieve a return to normality and overcome dysbiosis.

Several studies in recent years have shown the key role that probiotics have been playing in reestablishing the balance of the microbiota and thus preventing or controlling the development of certain comorbidities linked to dysbiosis such as: cancer [7], major immune system problems [3] or pathologies of the central nervous system [8]. In addition, they have proven immunomodulatory and gut barrier functions [9,10].

All these assumptions have established the need to understand in a concise manner the role that each bacterial genus plays within the body, in order to later face multiple diseases through more effective treatment. The large amount of funding received from European projects for the design of new probiotics reflects the need for a treatment that improves the approach towards different diseases, such as those related to diet or disorders related to the immune system, among others [11].

In the early 2000s, a detailed report was published by the WHO and FAO on the evaluation of probiotics [12]. In this report, probiotics were defined for the first time, and this approach was widely adopted and accepted. A more recent meeting held by the International Scientific Association for Probiotics and Prebiotics (ISAPP) decided to carry out a redefinition of what is meant by probiotics [13]. Specialists in all areas related to this concept (with specialties in gastroenterology, pediatrics, family medicine, gut microbiota, microbiology of probiotic bacteria, microbial genetics, immunology and food science) finally decided to define it as the set of “live microorganisms that, when administered in adequate amounts, confer a health benefit on the host”. More recently, SEPyP clarified that for a microorganism to be qualified as a probiotic, it is necessary to scientifically demonstrate that it has beneficial effects on human health [14]. The categorization of the strains is also considered of vital importance since the fact that a probiotic is effective for a specific pathology does not indicate that it is valid for other indications. In addition, it is important to differentiate the observed scientific evidence stratified by age and physiological states [15,16]. It is relevant to point out that there is a booming demand from the population for food products containing probiotics. In addition, pharmacists and physicians themselves have begun to recommend probiotics for the treatment of certain disorders. The data and studies on probiotic strains that have been published with clinical results are beginning to be abundant to such an extent that a professional in the field experiences difficulties in knowing all the available probiotic products with clinical evidence.
State of the Art

It is undeniable that increasingly more applications are being used to consult all kinds of information. The healthcare world is no exception, and is evolving towards a more technological approach, where there are more and more applications that support clinicians in diagnosing pathologies, making decisions and even prescribing medical treatment to ensure that the medication and its dosage are correctly indicated.

Currently, there is the Clinical Guide to Probiotic Products application, which is a Canadian guide to consult the scientific evidence available for probiotic products. It was created using published data from clinical studies for various probiotic strains [17]. Only commercial products available and approved in Canada were used in this application. There is also an American version created by the same authors, in which the probiotics that appear are those approved in the United States [18].

Although there are applications that allow consultation of the clinical evidence of probiotics, they only include those approved in Canada and the United States. The information they provide is very useful, but in countries such as Spain, the commercial products are not the same, and it would not be appropriate when recommending a probiotic to a patient for a given pathology.

2. Objective

The main objective of this work is to simplify the consultation process to the practitioners, so that with a simple software tool, agile and intuitive, the search and consultation of the adequate probiotic for a pathology is fast and effective. Doctors or pharmacists will have all the updated information about scientific publications, benefits of each probiotic to the different pathologies, allergens information of each probiotic, etc. to treat and advise their patients.

To achieve the objective of having a simple query method in our web tool, we have had the support of the authors of the first clinical guide based on scientific evidence for the supplementation of probiotics available in Spain [19].

Practitioners could consult practical and clinically relevant information on probiotics, allowing them to easily select the appropriate product, dose and format for a particular indication, without the slowness of the written guidelines, which do not facilitate a comfortable and fast decision making process.

3. Results

The development of a tool was proposed in order to consult which probiotic products are suitable for a specific pathology. The system is designed to be able to eliminate, modify or add pathologies, strains, probiotics and references.

3.1. Proposed Workflow

The application is organized according to the pathologies [20]. That is, depending on the problem that the patient has, a search for the right product to treat it will be carried out. Subsequently, one can see the composition of the probiotics, which are the commercial products that the professionals prescribe.

In this way, before prescribing a certain product, one will be able to see what allergens it contains and what strains it is made of. The term “strain” refers to a biological variety within a species; a species in turn exists within a genus. For example, for a given probiotic, the name *Lactobacillus acidophilus SD5212* tells us the name of the genus (*Lactobacillus*), the species (*acidophilus*), and the strain (*SD5212*). Different manufacturers of probiotics use different strains, although they may be of the same species and genus, meaning that one *L. acidophilus* supplement is not the same as another *L. acidophilus* supplement. Therefore, the best choice is a probiotic supplement that uses robust, well-researched strains. This is very important considering the latest pharmaceutical developments, as one can prescribe a probiotic, making sure that it is the right product.
The specialist could consult these recommended probiotics for each pathology according to the age range of the patient, differentiating between adults and children and among adults, with a special section for women’s health. There are studies that suggest that the human intestinal microbiome is relatively stable and adult-like after the first 1 to 3 years of life. Others suggest that the healthy pediatric intestinal microbiome harbors functional and compositional qualities differs from those of healthy adults, therefore, adults and children should be treated with different products [21].

In addition to this, there will be information on dosages. In this way, it will be possible to observe how often it is advisable to take the probiotic and for how long, or if one receives special recommendations or guidelines for taking it. In addition, one can see whether the product is available in capsules, pills, sachets, etc. Thanks to all this information, the patient will have well-defined guidelines for taking the probiotic. Furthermore, the application allows adding references of studies for authorized users, where the effectiveness of the dose of a product on a pathology is shown.

The entire previously described workflow is shown in Figure 2.

![Figure 2](image)

**Figure 2.** Entity relation model of the performance of the application.

As explained above, and as shown in Figure 2, the connections defined with the letters \(N\) and \(M\) refer to the sections that can contain more than one possible coincidence, for instance, the same probiotic can contain more than one allergen or strain; meanwhile, the connections that are connected with an \(N\) and 1, will be those where there is only one possible option, as with evidence and pathology; evidence of a specific dose of probiotic with its corresponding scientific references can only be associated with a pathology.

### 3.2. Prescription Assistance System

This paper presents the system **Probiotic** that was developed with the aim of providing a tool that includes the products endorsed in Spain for later consultation. The system includes preloaded probiotics, dosage, evidence and pathologies in the first clinical guide, based on scientific evidence for the supplementation of probiotics available in Spanish pharmacies [19]. Although the system contains Spanish probiotic products, there is no limitation to be used with probiotics from other countries, being only necessary to update the data.

Thus, first we opted for a development with free and multiplatform technologies, which allowed eliminating the use of licenses that can be deployed in any infrastructure without entailing any cost due to the use of the tool. The developed system has a website that allows remote consultation, in a very simple manner, of the appropriate probiotics for a particular pathology. Figure 3 shows what the homepage of the website that was developed would look like.
Figure 3. Main page of the site. From it, any user can start their search by indicating the type of pathology, and optionally, at the top, they can specify an age range.

Once the pathology has been selected, the available probiotics are shown, ordered by the level of evidence, and displayed in the manner shown in Figure 4. In this case, the pathology entered in the search engine was antibiotic-associated diarrhea, so the application will show the different probiotics associated with such pathology, along with the various specifications that have been discussed, and one can also select whether it is an adult or a child, thus adapting dosage and probiotic to each case.

Figure 4. Proposal page. Recommended probiotics for antibiotic-associated diarrhea are listed on the page.

In addition, the system developed is not intended to be static and has an administration panel that allows the user to create, edit or delete information of all kinds. Through there, the user is redirected to a window like the one shown in Figure 5, where one can access quick actions to view details, edit or delete. These features, depending on whether they are more or less sensitive, will be available for modification according to the type of user with whom one is accessing the site, as will be explained in the methodology section.
If one tries to open any of the probiotics once we have finished modifying them, all the data associated with them will appear in an organized manner, as shown in Figure 6, besides knowing who the last person to modify it was.

4. Discussion

From the beginning, a fundamental aspect has to be considered. It is essential for health professionals to have a reference point where they could check the information. The objective was never the design or the writing of a guide in a specific moment since new discoveries are constantly being made, leading to a need to continuously update the guide. That is why the application presented in this work was conceived. The advantage of having an application and not a paper document, is that new elements can be added anytime, such as more evidence or new strains. When new elements are added, users
can consult the information without having to take a proactive role in updating personal
guides that they could use as reference.

In addition, in order to consult the evidence of the relationship between probiotics and
pathologies, the application has a section of bibliographic references where one can consult
the studies claiming that a specific strain is beneficial for a particular pathology [19].

5. Materials and Methods

5.1. Materials

The tool has been developed following a methodology based on SCRUM and is
available at: https://gitlab.com/udc-stuff/probiotic/core [22]. In order to deploy the
application, one should configure the persistent storage, for which the relational database
MariaDB is used, which revealed that the entity-relation. It is not necessary to have the
tables created, because the application uses liquibase version control to apply the necessary
changes to the database (shown in Figure 2 [23]). In addition, the use of the ElasticSearch
engine is included to make text-based searches much more efficient [24].

Regarding the backend, the application is written in Java, since it enables indepen-
dence from the operating system and can be deployed in any environment. The front-end
is designed as a single page application developed in angular, and uses a RESTful API for
communication with the backend. API RESTful allows the query, insertion, modification
and elimination of all the entities that are stored; it is possible that the different centers can
collaborate with each other by implementing a simple script to load the information that
they consider to be appropriate [25].

Any medical, pharmaceutical or research center could deploy a private copy of the
application and dump the data they deem appropriate because the source code is available
to everyone. This allows them to use the infrastructure they deem appropriate, since
the deployment configuration is done through the application-prod.yml file used by spring
boot [26]. In this file you can modify the data to have a specific configuration of mariadb,
indicate the nodes of the elastic search cluster or even modify the authentication in JWT by
modifying its secret and for how long a token is valid. [27].

5.2. Methodology

The developed tool can be accessed by three different types of users: anonymous, user,
and administrator. The anonymous user is the one who does not need to be registered and
can consult the relationships between pathologies, evidence and information related to
probiotics. The other two types of roles, user and administrator, need to be registered in
the system, and the authentication system is based on JWT, which is stateless, allowing an
easy scale-out if it were necessary [28].

The user and administrator roles can perform all operations for anonymous users and
also have the privileges to create, modify or delete information. The difference between
them consists of the information they can modify. An administrator can modify sensitive
information or information that hardly varies, which allows for a more controlled access.
More specifically, an administrator can create, delete or edit the users of the platform,
as well as modify the roles. In addition, since the list of known allergens is limited, only an
administrator will be authorized to modify it.

Whoever has a user role can create, edit or delete the rest of the information, i.e., in-
formation about pathologies, evidence, strains, probiotics, doses, references and all the
relationships among them.

The procedure for adding the information to the tool is very straightforward. First,
one has to enter the entities and then the relationships among them. That is, one should
first add the entities that have no relationship with others, and later create the hierarchy
based on relationships, which implies that it will not be possible to create evidence if the
pathology or the dose of the probiotic has not been previously available. The methodology
suggested so that someone with the role of user can enter the information is the following:

1. Enter the pathology if it does not exist.
2. Add all the strains of probiotic that are not discharged into the system.
3. Enter the probiotic with its corresponding relationships (strains and allergens).
4. Specify the doses at which the probiotic can be administered (type of dose, quantity, and frequency).
5. Include the references that guarantee that the doses of a certain probiotic are adequate for a certain pathology.
6. Insert the evidence that relates all the information entered in the previous steps.

6. Conclusions

Given the current need to maintain the balance in the microbiome for human health, this research study is aimed at creating a collaboration tool so that professionals can help patients to achieve this. The initial proposal of this project was to develop an application capable of facilitating the consultation of probiotics associated with pathologies without having to resort to scientific documents and facilitating the search and consultation of information, achieving the main established objective.

A website system was built following a Java architecture through the implementation of the MVC pattern that allows managing all the information related to probiotics, strains, pathologies, scientific evidence, etc. [29].

To sum up, the users who tested this application considered that the project was developed in a satisfactory way, fulfilling our expectations and objectives. With the development of this tool, the first guide in Spain was created, being updated with scientific references, and bringing value to the research group, since computerizing and organizing all the information generated will help them to both improve the consultation and prescription of probiotics and continue with more rigorous research on the role of probiotics in order to control microbiota for improved disease treatment.

The current version of the developed system is fully functional. Some of the improvements considered to have greater potential and which are currently being implemented are:

- **Patients’ records**: To provide the application with a patient record through which the probiotics and medications prescribed for the patient could be registered and a more personalized follow-up could be done.
- **Improvement of the prescription system**: This option allows the system to recommend the probiotic or combination of probiotics that best covers the strains that are beneficial for the patient, in the event that a patient requires different probiotics for different pathologies.
- **Statistical analysis system**: To provide the application with a reporting tool which allows the study of different factors such as the most common pathologies or the most used probiotics.

Tools and initiatives of this type are necessary to generate standardized science-based mechanisms, with the benefits that they will bring to the future development of biomedical, pharmaceutical and clinical research.

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Abbreviations
The following abbreviations are used in this manuscript:

- WHO: World Health Organization
- FAO: Food and Agriculture Organization
- SEPyP: Spanish society of microbiota, probiotics and prebiotics (Sociedad Española de microbiota, Probióticos y Prebióticos)
- MVC: Model View Controller

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