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Online Database for Retrieval Information about Prebiotics and Their Activity

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Abstract: The number of studies aimed at proving the prebiotic properties of certain substances or compositions has been actively increasing, which has led to a large accumulation of scientific information that is fragmented and not systematized. Moreover, a number of criteria have been applied in these studies. The lack of an accessible and convenient information space to compare the obtained results seems to hold back not only scientific development, but also practical development in this field. A database called the «On-line Database of Researches on Activity of Prebiotics» (ODRAP) is presented in this article, which contains information about both prebiotics and some probiotics, that were used in these researches. Currently, ODRAP collects 25 bacteria genera or their combinations, 59 bacteria species, 140 prebiotic substances, 61 prebiotic production companies, 2 methods of fermentation, and 271 analyzed articles from 2001 till 2019. To facilitate access to the database, a special Web-interface was created, which allows any user who opens the Web-page to obtain information about the features and activities of prebiotics, as well as to sort the data by species and genus of bacteria applied in tests, the chemical nature or source of prebiotics, and other parameters. The convenience of the Web-interface is that it allows access to the database, regardless of the user platform and from anywhere, via the Internet.

Keywords: online database; web-interface; prebiotics activity; probiotics; synbiotic factors

1. Introduction

The human body is a complex system consisting of about 10^{14} microbial cells interacting with the host [1,2]. The essential role of the gut microbiota for health has generated tremendous interest in modulating its composition and metabolic function. One of these strategies is using prebiotics, which typically refers to selectively fermented non-digestible food ingredients or substances that specifically support the growth and/or activity of health-promoting bacteria (probiotics) that colonize the gastrointestinal tract [3–5]. As noted by Hill C. et al. [6] probiotics are «live micro-organisms which when administered in adequate amounts confer a health benefit on the host. Prebiotics were defined as a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, and thus improves host health» [7]. There are number of information systems and databases which have made it possible to collect various microbiological data, among which online databases should be highlighted [8–12].

The main purpose of Online Databases and Internet resources for science is to group data together and provide URLs and hyperlinks, such that any researcher, teacher, or student can access them with minimal effort, time, and cost [13,14]. However, there are not a lot of databases or information systems in the fields of prebiotics and related to probiotics. A probiotics database named PROBIO was developed to facilitate these efforts and to address the need for information on the known probiotics, providing comprehensive information about the functions of marketed probiotics, clinical/field trials, and research probiotics for use or being studied for use in humans, animals, and plants [15]. This probiotic databases are typically focused on clinical research *in vitro* or animal studies. The probiotic database PBDB [16] includes information about different probiotics sourced from fermented foods. Information about other Probiotics databases has been presented by the Probiotic Professionals site, where the most researched probiotic strains in the world are collected [17]. The strains have been chosen due to both the quantity and quality of the research behind them, but mainly by the quality. Some Web-sites of organizations specialize in the investigation of probiotics and prebiotics, such as that of the Global Prebiotic Association [18], where links on this theme have been collected.

When considering prebiotics, it is necessary to pay great attention to their activity, which is an important task for estimating the perspectives of using such substances as prebiotics. There are different methods to evaluate prebiotic activity. The most commonly used technique for prebiotic activity evaluation *in vitro* is based on the fermentation of mixed faecal cultures of healthy donors, which was first applied by Japanese researchers in the 1980s [19]. Simple batch fermentations are carried out and the pH is kept under control or not. Non-cultural methods of bacteria enumeration, such as fluorescence in situ hybridization (FISH) and polymerase chain reaction (PCR), have greatly enhanced the accuracy of prebiotic activity assessment. The range of analyzed prebiotics has been greatly expanded recently: exopolysaccharide from *Cordyceps sinensis* Cs-HK1 [20], xylooligosaccharides produced by *Bacillus subtilis* 3610 [21], extracts of brown seaweed [22], and so on. Basing on the data obtained from the fermentation of fecal cultures, Palframan, Gibson, and Rastall [23] suggested calculation of a prebiotic index (PI), which was determined as the difference between the number of probiotics and non-probiotics at the end of the fermentation. Vulevic, Rastall, and Gibson [24] replaced the number of bacteria by the specific growth rate, which demonstrated the relationship to the kinetic patterns of micro-organism growth; however, the mechanism of their interaction in a mixed culture remains hidden. The prebiotic index has been used, for example, to study wheat food grade curdlan (1->3)-beta-D-glucan) from *Alcaligenes faecalis* [25] or oligo-glucomannan from *Amorphophallus konjac* [26]. The "useful" bacteria (typically, *Bifidobacterium* and *Lactobacillus* genera) from faeces are took into account in the mentioned techniques, not pure cultures of probiotics. The "harmful" *Clostridium* and *Bacteroides* are commonly recognized as antagonists, means that their specific growth rates are included in the equation with "minuses". This approach is related to the prebiotic concept. Moreover, as Palframan et al. pointed [23], PI allows to compare the results of different researches on prebiotics.

Methods for prebiotic activity evaluation which apply pure cultures are not utterly informative, as it is not possible to take into account the interaction of bacteria. However, Huebner et al. [27] proposed a quantitative measure of prebiotic activity, the prebiotic activity score. Its dimension is based on the comparison of specific growth rates. The prebiotic activity score is less common, although it has been used in a number of studies [28–31]. The well known probiotic bacteria such as *Bifidobacterium lactis* subsp. *animalis* Bb-12 or *Lactobacillus rhamnosus* GG, are commonly used. So called enteric mixture (a lot of *Escherichia coli* strains) is supposed as antagonists. One of the most common models of the intestine is a three-stage continuous culture, as proposed by Macfarlane et al. [32]. Using this method, the prebiotic effect, which has also been associated with an increase in the number of probiotics and production of SCFA, has been evaluated, for example, for mixture of galactooligosaccharides, lactose, glucose and galactose (B-GOS) [33] and fructans with differing in degree of polymerization [34]. 'A mixture of synergistically acting probiotics and prebiotics' has been defined as synbiotics [7]. Synbiotics incorporate the properties of probiotic and prebiotic ingredients and provide a greater effect than that of the probiotics or prebiotics separately. One of approaches to assessing such synergism *in vitro* is the co-culturing of probiotic bacteria with selected pathogens in prebiotic contained media [35–38].

The criteria obtained from a quantitative model of co-culture has been suggested for the comparison of symbiotic activity against pathogens in different conditions [39]. Analysis of existing databases on prebiotics and probiotics has shown that there are no such databases containing information about prebiotic activities and the methods for their evaluation. In this paper, a developed online database (ODRAP) is presented, which includes unique content concerning different probiotics and prebiotics, along with their activities.

2. Materials and Methods

The database was implemented using MS Office Access 2013 (https://products.office.com/ru-ru/access/). The Web-interface was written using the programming language Python (https://www.python.org/) and technology with the Django framework (https://www.djangoproject.com/). For the client part, HTML (http://htmlbook.ru/html), CSS (https://drafts.csswg.org/), Javascript, and js, as well as the Vue.js library, were used. The ODRAP database is freely available at https://rs-pharmcenter.com/rnf2019/db2/index.html?page=1.

3. Results

3.1. The ODRAP Database

Conceptual and logical models of the database were first developed. The *in vitro* studies were our main focus. Database tables were attached to each object in the conceptual model, containing the corresponding object attributes, and relationships between tables in the logical model were established using primary keys. This is reflected in the infological diagram of the database (Figure 1) which reflects the relationships between these data groups were defined. One medium can be applied for the fermentation of different probiotics, a given probiotic can be used with different prebiotics, one cultivation method can be applied to different prebiotics, one set of metabolites can be suitable for different prebiotics, and so on [40,41].

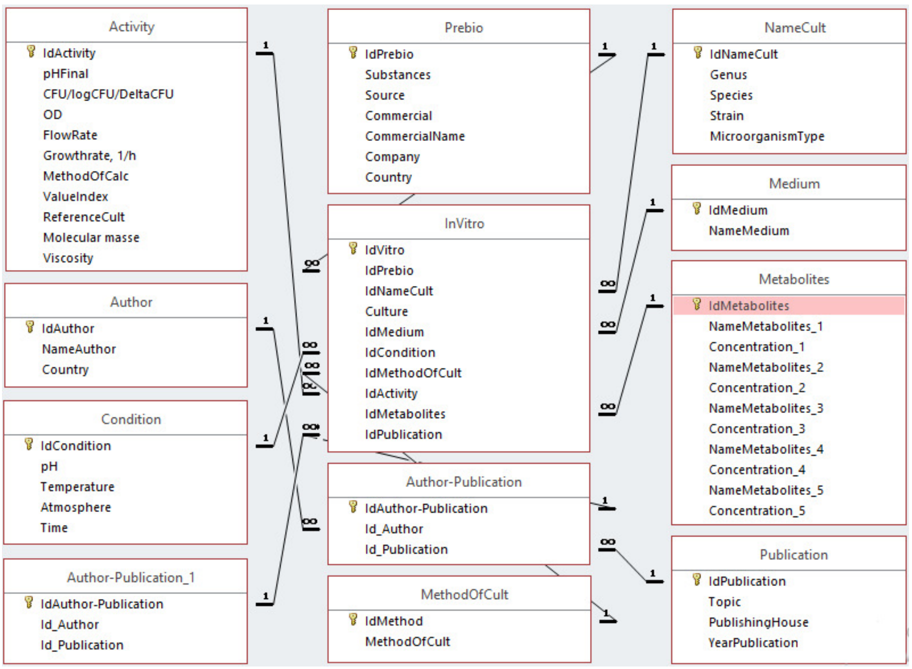

Figure 1. Infological diagram of the database, which reflects the relation between all data groups (1 means one parameter from one group, ∞ means many different parameters from another group, for example, one medium can be applied for the fermentation for different prebiotic tests).

The database includes 12 main and auxiliary tables which describe the parameters of the main elements. The table «Activity» (Figure 2) contains information about the main physiological features of the micro-organisms [42–44]. Such parameters as final pH of fermentation, viable micro-organisms count, optical density, and information about the flowrate and growth rate, as well as methods for prebiotic activity definition: prebiotic activity score (PAS), measure of the prebiotic effect (MPE), prebiotic index (PI), synbiotic index (SI), and synbiotic factor (SF), are highlighted [45].

Activity

IdActivity	pHFinal	CFU/logCFU/DeltaCFU	OD	FlowRate	Growthrate, 1/h	MethodOfCalc	ValueIndex	ReferenceCult
65		7.84						
66		8.87				Prebiotic activity score	1.2	
67		9.02				Prebiotic activity score	1.69	
68		7.42				Prebiotic activity score	0.03	
69		10.33				Prebiotic activity score	1.69	
70		10.26				Prebiotic activity score	1.44	
71		9.53				Prebiotic activity score	0.25	
72		3.09			0.25			
73		2.5			0.24	Prebiotic activity score	0.54	
74		2.01			0.08	Prebiotic activity score	0.41	
75		2.44			0.07	Prebiotic activity score	0.55	
76		2.49			0.54	Prebiotic activity score	0.56	
77		2.41			0.14	Prebiotic activity score	0.54	
78		1.8			0.09	Prebiotic activity score	0.3	
79		2.34			0.19	Prebiotic activity score	0.53	
80		2.52			0.14	Prebiotic activity score	0.57	
81		1.5			0.3	Prebiotic activity score	0.2	
82		2.4			0.14	Prebiotic activity score	0.54	
83		1.93			0.11			
84		0.96			0.26	Prebiotic activity score	0.23	
85		0.69			0.08	Prebiotic activity score	0.1	
86		0.56			0.04	Prebiotic activity score	0.05	
87		1.56			0.06	Prebiotic activity score	0.56	
88		0.52			0.04	Prebiotic activity score	0.03	
89		1.76			0.06	Prebiotic activity score	0.63	
90		0.45			0.03	Prebiotic activity score	-0.01	
91		1.48			0.1	Prebiotic activity score	0.53	
92		1.74			0.13	Prebiotic activity score	0.62	
93		0.48			0.02	Prebiotic activity score	0.01	
94					0.13			
95					0.21			

Figure 2. Table «Activity» containing information about the main physiological parameters of the micro-organisms growth on prebiotics (for example, final pH of fermentation, viable micro-organisms count, different methods for prebiotic activity definition and etc.).

The cultivation conditions are contained in the table «Condition», which are pH, temperature, atmosphere, and time [46,47]. Figure 3 «Prebio» is key table stored data on prebiotic substances, source of origin, and information about manufacturer. Data on microbiological cultures and their features are concentrated in the table «NameCult» (Figure 4). In this part of the database, various types of micro-organisms, their genus, species, and strains are considered. For the methods using faecal cultures *Bifidobacteria* and *Lactobacillus* were indicated as probiotics. Although assumption is rather conditional it was introduced considering that the increasing of such bacteria count is associated with benefits for the human. Moreover, it was decided to simplify the structure of database. The following micro-organisms were taken into account for the methods based on the pure cultures fermentation: *Bifidobacterium animalis* Bb-12, *Lactobacillus rhamnosus* GG, *Bifidobacterium bifidum*, *Lactobacillus plantarum*, and so on. The test cultures for PAS or SF evaluation were recognized as probiotics by authors. While filling the tables, popular commercial probiotic micro-organisms were taken into account, as well as variants of mixed types developed by various researchers [48].

The table «Author-Publication» allows connection between the tables «Author» and «Publication». These tables contain information about manuscripts published mainly over the past 20 years, including the name of author, title, topic and year of publication, title of journal, for example, Journal of functional foods, and etc. The table «In vitro», being the key table, joins the main information from the tables «Prebio», «NameCult», «Medium», «Condition», «Activity», «Metabolites», and «Author-Publication». Currently, ODRAP collects 25 bacteria genera or their combinations, 59 bacteria species, 140 prebiotic substances, 61 prebiotic production companies, 2 methods of fermentation, and 271 analyzed articles. Thus, the created database allows users to sort and systematize the necessary data on probiotics, both known and created by experts, and about various substances that can serve as prebiotics. The advantages and key point of the ODRAP database is the information concerning prebiotic activities and various methods of their assessment. This database will allow for analysis and comparison of a lot of data to improve future research.

Prebio

Substances	Source	Commercial	CommercialName	Company	Country
Fructooligosaccharides	chicory	Yes	Raftilose P95	Orafti	Belgium
Fructooligosaccharides	agava	No			
Fructooligosaccharides	cane sugar	Yes	NutraFlora P-95	Golden	USA
Xylooligosaccharide		Yes	XOS Longlive 95P	Shandong Biotechnology	China
Inulin	chicory	Yes	Inulin-S	Sigma-Aldrich	UK
Glucose		No			
Inulin	chicory	Yes	Raftiline HP	Orafti	Belgium
Galactooligosaccharide		Yes	Purified GOS	Yakult Pharmaceutical Ind.	Japan
Inulin	agava	Yes	Inylin HP	Orafti	Belgium
Synergy1	agava	Yes	Synergy1	Orafti	Belgium
Oligofructose	agava	Yes	Raftilose P95	Orafti	Belgium
ScFOS	agava	Yes	Actilight 950P		France
Cellulose	agava	Yes		Sigma-Aldrich	UK
Longan DH 21	longan	No			
Longan DH 0	longan	No			
Anco Marzio	triticum turgidum ssp. Du	No			Italy
Claudio	triticum turgidum ssp. Du	No			Italy
Iride	triticum turgidum ssp. Du	No			Italy
Levante	triticum turgidum ssp. Du	No			Italy
Orobel	triticum turgidum ssp. Du	No			Italy
Solex	triticum turgidum ssp. Du	No			Italy
Svevo	triticum turgidum ssp. Du	No			Italy
Khorasan	triticum turgidum ssp. Tu	Yes	Kamut		USA
Urria	triticum turgidum ssp. Du	No			
Senatore Cappelli	triticum turgidum ssp. Du	No			Italy
Sucrose		Yes		Sigma-Aldrich	UK
Guar gum		Yes		Sigma-Aldrich	UK
Sunfiber (HM 1)		Yes		Taiyo Kaguku	Japan

Figure 3. Table «Prebio» containing the key data on prebiotics-substance, source of origin, and information about manufacturer. The cell "Commercial" was filled by value "no" if new, non traditional sources of prebiotics was applied in the researches. This should help the users to recognize the features of some plants.

NameCult

IdNameCult	Genus	Species	Strain	Microorgani
1	Bifidobacterium	bifidum	NCI	Probiotic
2	Escherichia	coli		No probiotic
3	Bifidobacterium	adolescentis	ATCC 15706	Probiotic
4	Bifidobacterium + Lactobacillus		faecal	Probiotic
5	Bacteroides + Clostridium		faecal	No probiotic
6	Bifidobacterium		faecal	Probiotic
7	Bifidobacterium	longum	15708	Probiotic
8	Bifidobacterium	adolescentis	15706	Probiotic
9	Bifidobacterium	infantis	17930	Probiotic
10	Bifidobacterium	breve	15698	Probiotic
11	Lactobacillus	acidophilus	33200	Probiotic
12	Lactobacillus	acidophilus	NCFM	Probiotic
13	Lactobacillus	plantarum	12006	Probiotic
14	Lactobacillus	plantarum	4008	Probiotic
15	Lactobacillus	paracasei	1195	Probiotic
16	Lactobacillus	plantarum	L12	Probiotic
17	Bifidobacterium	pseudocatenulatu	B7003	Probiotic
18	Lactobacillus	acidophilus	La5	Probiotic
19	Bifidobacterium	lactis	Bb12	Probiotic
20	Escherichia	coli	ATCC 25922	No probiotic
21	Bifidobacterium		Bif 164	Probiotic
22	Lactobacillus		Lab 158	Probiotic
23	Escherichia	coli	ATCC 25645	No probiotic
24	Klebsiella	pneumoniae	GC 23a	Pathogen
25	Enterobacter	cloacae	GC	No probiotic
26	Eubacterium	rectale	Erec 482	No probiotic
27	Bacteroides		Bac 303	No probiotic
28	Clostridium	histolyticum	Chis 150	Pathogen
29	Escherichia	coli	Ec 1531	No probiotic

Figure 4. Table «NameCult» containing the information about various types of micro-organisms.

3.2. The Web-Interface

The specially written Web-interface allows a user who opens a Web-page to become familiarized with information on prebiotics and their activities, sort by type and genus of probiotic, and other parameters [49]. The Web-application connecting to the database server consists of client and server parts [50]. The client part implements the user interface, while the server part receives and processes queries from the client, performs calculations, forms a Web-page, and sends it to the client according to the HTTP protocol. The programming language Python and the Django framework were used to create the server part [51]. HTML, CSS, JavaScript, and the library Vue.js were used for the client part [52,53]. The client application allows a user to use the following search parameters:

- bacteria genus;
- bacteria species;
- prebiotic substances;
- company producer of prebiotic;
- method of fermentation; and
- author of article.

Figure 5 shows the main page of the Web-application. Access is provided through a browser (e.g., Internet Explorer, Edge, Safari, Firefox, or Chrome). In the browser, a Web-page can be opened by entering the following URL: https://rs-pharmcenter.com/rnf2019/db2/index.html?page=1. On the left side of the main page of the Web-application, the search options can be found. These parameters can be selected both individually or together, depending on the task. The Figure 6 is example of search on prebiotic substances. FOS (fructo-oligosaccharides) was selected as prebiotic substance. In ODRAP database 64 records with it were found. On the Figure 7 the example of search on author of article is shown. If the name Gibson G.R. will be selected 212 records could be found.

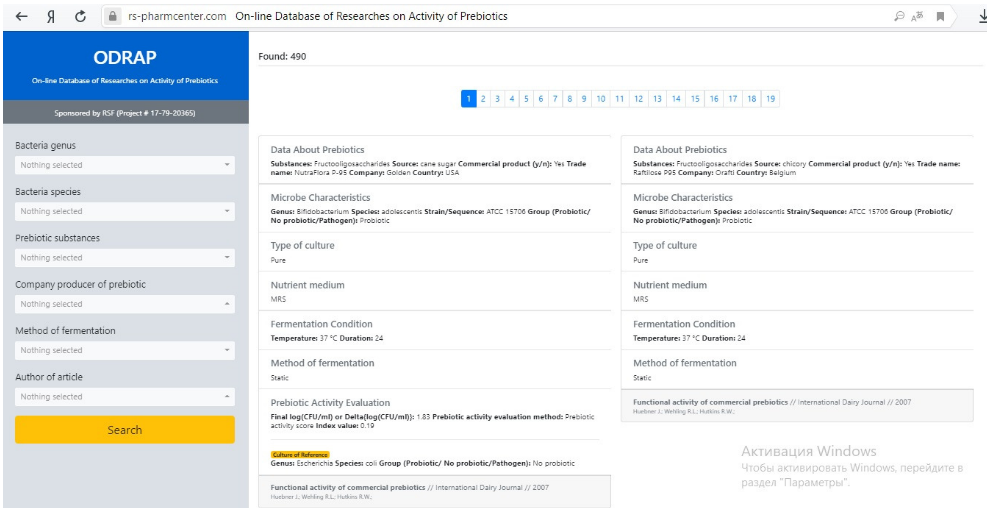

Figure 5. The main page of the Web-application of ODRAP database.

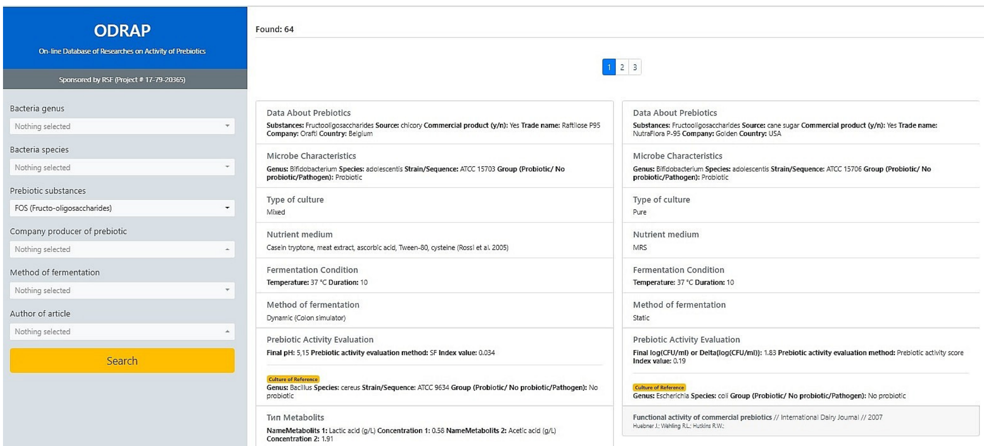

Figure 6. Example of search: FOS (fructo-oligosaccharides) was selected as prebiotic substance, 64 records with FOS were found.

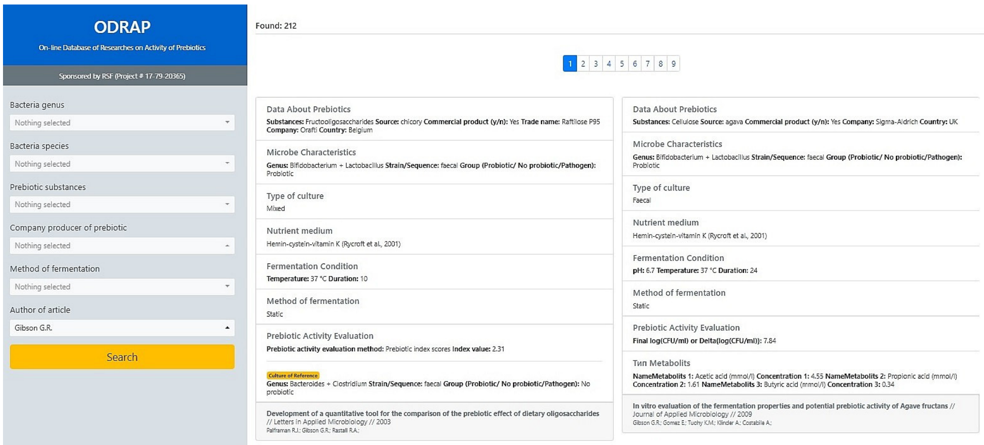

Figure 7. Example of search: the name of author of article is Gibson G.R., 212 records could be found.

Besides, it could be possible to make a joint search (Figure 8). The search query was on 3 search parameters:

- bacteria genus: Bifidobacterium+Lactobacillus+Eubacteria;
- author of article: Chaiongharn A.;
- method of fermentation: Static.

As a result, six prebiotics were found.

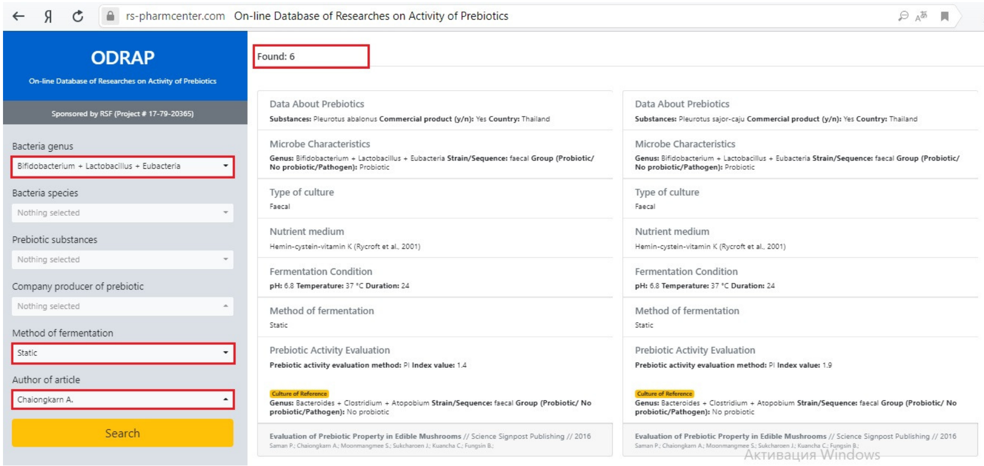

Figure 8. Result of joint search: 3 search parameters were: bacteria genus—"Bifidobacterium+Lactobacillus+Eubacteria", author of article—"Chaiongharn A.", method of fermentation—"Static". As a result, six prebiotics were found.

Figure 9 illustrates the criteria SF obtained from the quantitative model of co-culture suggested for comparison of symbiotic activity against pathogens in different conditions [35].

Access to viewing information in the database is opened to any user by entering the following URL: https://rs-pharmcenter.com/rnf2019/db2/index.html?page=1. Entering, changing and deleting data is possible only through the database server. The database server is managed by the administrator, who has full rights to create, modify and delete data, and can provide users with access rights to manage data through an account. Currently, only a limited number of users have permission to the server. In the future, manage to the database server can be expanded for users through a registration form with the ability to enter information. This will protect against unauthorized copying, modification or exception of database records and tables.

Thus, by means of the Web-application of ODRAP database, a user can obatin information on the specific concerning the fields of prebiotics and their activity used with a number of probiotics.

It should be mentioned that the main advantage of the Web-application is the fact that it does not depend on a particular operating system, as Web-applications are cross-platform services.

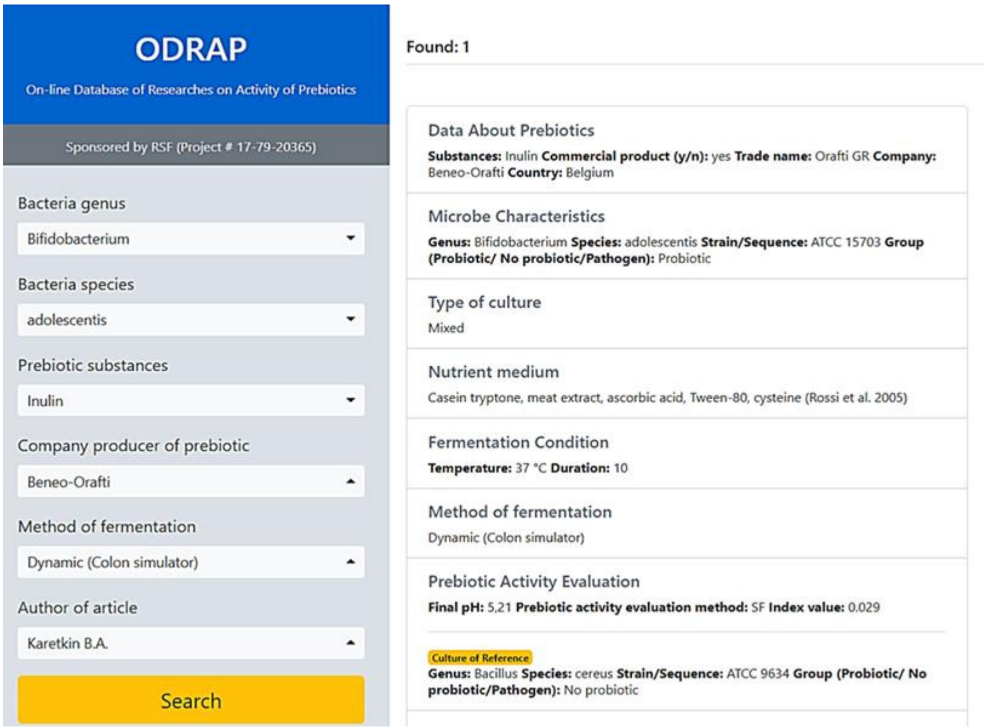

Figure 9. Example of search: synbiotic factor SF obtained from the quantitative model of co-culture suggested for comparison of symbiotic activity against pathogens in different conditions [35].

4. Conclusions

In this paper, we present the ODRAP database, which is based on the information of articles by various researchers and implemented using MS Office Access 2013 [54,55]. The implemented database is specific and it was assigned for the scientists working in microbiology and biotechnology. This database allows to search for necessary information concerning prebiotics and their activity by definite parameters. The advantage of using MS Office Access 2013 is its integration into desktop PCs, ability to export and convert data, and a wide range generation of forms, reports, and queries which can be used to sort data and enter it in a convenient manner [56]. This data structure is unique, as it contains information about the assessment of prebiotic activities *in vitro* and the different methods used to define them. A Web-application, with a user-friendly Web-interface, was implemented for convenient user access to the database, which provides the ability to search for information in a specific direction and priorities in the fields prebiotics and their activity [57,58]. A Web-interface passed the test period and was approved by our colleagues. It is planned to update this version of ODRAP database after receive sufficient statistics on navigation adjustments and recommendations. The implemented database will be updated depending on the accumulation of data on research in this field. The ability to upload new information in the database by users or researchers has great prospects and allows to increase speed of data update. However, the significant redesign of the interface and the development of data verification system are required. Currently, ODRAP collects information 25 bacteria genera or their combinations, 59 bacteria species, 140 prebiotic substances, 61 prebiotic production companies, 2 methods of fermentation, and 271 analyzed articles from 2001 till 2019. Criteria such as PI, PAS or SF can be compared using ODRAP database for the same prebiotic substances, but for different probiotic bacteria, or for substances of a similar nature obtained from different sources. In addition, such important information for the scientist working in microbiology as the production of metabolites (organic acids), which largely determine the suppression of the growth of pathogens, can be taken into account. In present version of the DB *in vitro* studies of prebiotic activity are included, as they are more numerous. In the future the DB can be expanded with data obtained in animals and humans studies *in vivo*.

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Abbreviations

The following abbreviations are used in this manuscript:

PAS	Prebiotic activity score
MPE	Measure of the prebiotic effect
PI	Prebiotic Index
SI	Synbiotic index
SF	Synbiotic factor

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