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USE OF PROBIOTICS IN COMMUNITY PHARMACY IN SOUTH AFRICA: A SURVEY OF PHARMACIST ATTITUDES, PERCEPTIONS AND KNOWLEDGE



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A dissertation by monograph submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree of Master of Pharmacy
Johannesburg, 2024

DECLARATION

I, Yedam Kim, student number [1825217], declare that this dissertation represents my own work. I made adequate contributions towards research findings published in the article stated below which are included in my dissertation. This dissertation is being submitted to satisfy the requirements for the degree of Master of Pharmacy at the University of the Witwatersrand, Johannesburg. It has not been submitted previously for any degree or examination at this university or any other institution.

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ABSTRACT

There has been a substantial increase in the consumption of probiotics in the last decade in South Africa. Pharmacists, as experts in the field of medicine, play a crucial role in educating both patients and other healthcare professionals on the appropriate use of probiotics in the healthcare setting. While there are several studies related to the use of probiotics, such as the study conducted among community pharmacists to explore their knowledge, attitudes, and practices regarding complementary and alternative medicines in South Africa, there is a gap in the literature regarding the knowledge, attitudes, and perceptions of qualified practicing pharmacists in South Africa regarding probiotic use. The findings of this study provide information for evaluating the current state of awareness and understanding regarding probiotics within the pharmacist community, offering a foundation for potential interventions and educational initiatives.

A cross-sectional, descriptive-analytical study was conducted in community pharmacies across South Africa. Of the 476 study respondents, 237 were included in the final analysis, as 239 surveys were incomplete. Among the respondents, 18.5% demonstrated a good level of knowledge about probiotics, while 11.3% demonstrated a poor level of knowledge (Mean ± SD =13.81 ± 2.8). This finding demonstrated a lower knowledge level compared with similar studies conducted in other regions, such as Asia and the United States of America. These findings highlight a potential gap in knowledge among the respondents regarding the use of probiotics. Half of the respondents (49.9%) displayed positive attitudes toward probiotics (Mean ± SD = 43.33 ± 8.9) and 47.6% of the respondents displayed positive perceptions of probiotics (Mean ± SD = 32.14 ± 3.7). A significant association of knowledge of probiotics with biological sexes ($X^2 = 39.2132$, $p < 0.05$) was found. There was a statistically significant difference in the demographics of respondents and their attitudes towards probiotics, including geographical region ($X^2 = 300.629$, $P<0.05$), biological sex ($X^2 = 95.164$, $p < 0.05$), age ($X^2 = 248.008$, $p < 0.05$), highest degree obtained ($X^2 =191.428$, $p < 0.05$), and the university from which they graduated ($X^2 = 417.775$, $p < 0.05$). Statistically significant difference in the demographics of respondents and the perceptions of probiotics was found, including geographical region ($X^2 = 170.161$, $p < 0.05$), age ($X^2 =52.378$, $p < 0.05$), and the university from which they graduated ($X^2 = 238.514$, $p < 0.05$. In this study, a significant but weak correlation between knowledge and attitude was identified ($r = 0.1537$, $p = 0.0179$). Correlation

between attitudes and perception was also significant but weak ($r = 0.3214$, $p = 0.000$) and there was no statistically significant correlation between knowledge-perceptions variables ($r = 0.0092$, $p = 0.8879$).

The study has identified limited knowledge regarding the use of probiotics among respondents, despite their positive attitudes and perceptions towards the use of probiotics. The study also has emphasized the complexity of factors influencing individuals' knowledge, attitudes and perceptions regarding probiotics. This study recommends further educational initiatives to investigate relationship between knowledge, attitudes and perceptions of pharmacists on the use of probiotics in South Africa.

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I express my sincere gratitude to my supervisors, Dr. Ané Orchard, Mr. Muhammed Vally, and Mrs. Razeeya Khan, for their invaluable guidance and support throughout the course of my dissertation.

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LIST OF ABBREVIATIONS

CFUs	Colony Forming Units
GPPSA	Good Pharmacy Practice South Africa
SAHPRA	South African Health Products Authority
FAO/WHO	Joint Food and Agriculture Organisation of the United Nations and the World Health Organisation
WGO	World Gastroenterology Organisation
BMI	Body Mass Index
GLAD-P	Guidelines for Allergic Disease Prevention
IBD	Inflammatory Bowel Disease
AGA	American Gastroenterological Association

DISSERTATION STRUCTURE

A dissertation was undertaken and comprises of the following chapters

- Chapter one introduces the study and explains the design.
- Chapter two provides a literature review.
- Chapter three provides the study entitled, ‘Use of probiotics in community pharmacy in South Africa: a survey of pharmacist attitudes, perceptions and knowledge.’
- Chapter four concludes the study.

CHAPTER 1 - INTRODUCTION

1.1 Background

Probiotics are defined as living micro-organisms that positively affect the bowel micro-ecology and health conditions (Fuller, 1991). Probiotics strengthen the mucosal barrier, compete for adhesion sites in gastrointestinal linings, and confer an immunomodulatory effect on the host (Papastergiou *et al.*, 2014). Several studies highlight the possible role of probiotics in alleviating immune system-related disorders, cardiovascular health, cancer, obesity, and psychological disorders (Yu and Li, 2016, Kerry *et al.*, 2018, Kothari *et al.*, 2019).

Therapeutic effects of probiotics also include alleviating the symptoms of adverse effects resulting from the pharmacological treatment of certain health conditions, such as *Helicobacter pylori* infections (Ayala *et al.*, 2014, Goderska *et al.*, 2018, Silva *et al.*, 2020, Yang *et al.*, 2020). The American Gastroenterology Association stated in their *H. pylori* clinical guideline that the consumption of probiotics resulted in enhanced patient tolerance of the antibacterial therapy of *H. pylori* infections (Lau *et al.*, 2016, McFarland *et al.*, 2016, Feng *et al.*, 2017). Studies have also reported that probiotics assist in reducing the frequency of diarrhoea caused by the use of antibiotics (Islam, 2016, van Wietmarschen *et al.*, 2020).

The use of antibiotics over several decades has been found to cause several drug-related problems such as drug-specific adverse effects and the emergence of multidrug-resistant bacteria (Yang *et al.*, 2020). Resistance to antibiotics has become a global issue due to an increase in antibiotic consumption (Guevara and Cogdill, 2020). The development of resistant bacteria has resulted from the frequent use of broad-spectrum antibiotics in human medicine and the irrational use of antibiotics for commercial purposes (Nami *et al.*, 2015). Since micro-organisms have the capacity to transfer antibiotic resistance, probiotics are also possible sources for antimicrobial resistance (Daniali *et al.*, 2020). Antibiotic resistance can be transferred to human intestinal pathogens when consuming certain probiotic strains (Belletti *et al.*, 2009). Although it is generally accepted that probiotics have good safety profiles, the transference of antibiotic resistance genes may represent a safety issue (Gueimonde *et al.*,

2013), thus bacteria in probiotics for humans should not contain any antibiotic resistance genes (European Food Safety Authority, 2008).

The use of probiotics is common, however, patients often do not discuss the use of probiotics with their health care providers (Chin-Lee *et al.*, 2014). Therefore, healthcare providers including pharmacists need to have sufficient information on the use of probiotics to provide evidence-based information to patients (Chin-Lee *et al.*, 2014). Pharmacists have a role in decreasing medication-related errors and optimising antimicrobial use. For instance, studies have shown that clinical pharmacists reduce problems related to efficacy and monitoring-related treatment problems (Wang *et al.*, 2010, Cioffi *et al.*, 2012, Abbas, 2014, Al-Somai *et al.*, 2014). It is recommended that evidence-based practices must be conducted by pharmacists on all products in pharmacies (Toklu, 2015). The minimal evidence supporting the specific use of probiotics should be acknowledged by healthcare professionals, leading to a necessity for additional research to improve their knowledge on the use of probiotics.

1.2 Probiotic Use

Legislation

A study done to assess probiotics manufactured in South Africa showed that some of the probiotic products on the market mislead consumers with claims that lack scientific substantiation and fail to adhere to the regulations outlined in the South African regulations in the Foodstuffs, Cosmetics and Disinfectants Act (Act No. 54 of 1972) (Brink *et al.*, 2005). The Good Pharmacy Practice South Africa (GPPSA) states that a pharmacist's first concern must be the welfare of the patient (GPPSA, 2017). Even though probiotics are not regulated by the South African Health Products Authority (SAHPRA), pharmacists are responsible for evidence-based decision making when providing probiotic supplements to patients. Despite a substantial increase in consumption of probiotic in the last decade in South Africa (Research and Markets, 2022), current pharmacist knowledge, attitudes and perceptions of probiotic supplements has not been studied.

International studies on probiotic use

While there have been limited international studies specifically focused on the use of probiotics by pharmacists, existing research conducted globally has consistently concluded that it is

crucial for health practitioners, including pharmacists, to provide scientifically validated recommendations on the selection of probiotics (Amarauche, 2015, Soni *et al.*, 2018a, Fijan *et al.*, 2019, Al-Qysi *et al.*, 2020). For example, a study conducted in Nigeria to assess the awareness and knowledge of the use of probiotics by healthcare practitioners found that only 16.3% of the participants responded that they knew of any research on probiotics. Of the 73 participants who were aware of any probiotic products available, 57.5% were pharmacists (Amarauche, 2015), however, all the pharmacists wanted more information on probiotics despite the available scattered scientific literature on probiotics. Another study conducted in Nigeria revealed that pharmacists had the second-highest level of knowledge after medical doctors, however, less than half of the pharmacists (44.1%) demonstrated a good level of knowledge (Chukwu *et al.*, 2015). A study conducted among physicians and clinical pharmacists in Jordan has concluded that healthcare professionals possess limited knowledge of probiotics, despite having positive attitudes toward them (Ababneh *et al.*, 2020). Furthermore, surveys conducted among healthcare professionals including pharmacists in Ahmedabad, India revealed that only half (54.6%) of the participants were familiar with information about the benefits of probiotics (Soni *et al.*, 2018b). The cross-sectional study conducted in Pakistan highlighted that a small proportion of healthcare professionals, specifically 15.1%, exhibited good knowledge about the use of probiotics, and a similar percentage, 15.6%, demonstrated good practices (Arshad *et al.*, 2021). Among healthcare professionals, pharmacists showed a significant association with both good knowledge and good practices (Arshad *et al.*, 2021). The study identified the lack of knowledge about probiotics as a significant barrier to probiotic use and as such, the study recommended the initiation of targeted training programs by professional health organisations to address this knowledge gap and enhance probiotic use among healthcare professionals (Arshad *et al.*, 2021). In contrast, an international study, including 30 countries in Western Europe, Central and Eastern Europe, and Australia revealed that pharmacists displayed a high level of familiarity concerning probiotics, encompassing details about specific strains and their mechanisms of action (Fijan *et al.*, 2019). The study attributed this to the fact that most probiotic products are accessible over-the-counter in pharmacies, requiring pharmacists to have a comprehensive understanding for informed consultations with their patients (Fijan *et al.*, 2019). The respondents in this study may have exhibited a higher familiarity with probiotics, potentially due to a greater emphasis on pharmacist-patient consultations and a more extensive market for

probiotic products in the regions (Stanton *et al.*, 2001, Anukam *et al.*, 2006, Oliver *et al.*, 2014, Fijan *et al.*, 2019).

Studies on probiotic use in South Africa

In South Africa, there has been no study conducted on the use of probiotics by pharmacists, therefore it is integral to discover pharmacist knowledge, attitudes and perceptions of probiotics, the rationale behind the selection and recommendation of a probiotic supplement, whether training was received on the use of probiotics, and the risks and benefits of probiotics.

1.3 Problem statement

Pharmacists, being experts in medicines, play a major role in educating patients and other healthcare professionals on the use of probiotics in the healthcare setting (Amarauche, 2015). Pharmacists are responsible for providing all products at the pharmacy based on evidence (SAPC, 2017). In South Africa, the probiotics market is anticipated to expand at a compound annual growth rate of 8.2% by 2029 (Research and Markets, 2022), however, knowledge, attitudes and perceptions of probiotic supplements has not been studied. The limited research on probiotic use in South Africa highlights the critical need to investigate various aspects related to the understanding of pharmacists on the use of probiotics. This includes understanding decision-making processes behind recommending or selecting a probiotic supplement by pharmacists, their level of education in probiotics, and their comprehension of the associated risks and benefits.

1.4 Research question

What are the attitudes, perceptions and knowledge of pharmacists on the use of probiotics in community pharmacies in South Africa?

1.5 Aim and objectives

This study aimed to determine the pharmacist's knowledge, attitudes and perceptions toward the use of probiotics in community pharmacies in South Africa via a survey.

The aim of the project was met by addressing the following objectives:

1. To investigate the community pharmacists' knowledge, attitudes and perceptions on the use of probiotics amongst their patients, via a REDCap® descriptive survey.

2. To investigate whether a relationship exists between participant demographics and the knowledge, attitudes and perceptions of participants towards probiotics.

3. To investigate whether a relationship exists between the participants knowledge and their attitudes or perceptions towards probiotics.

1.6 Purpose of Study

The finding of this study will provide information for evaluating the current state of awareness and understanding regarding probiotics within the pharmacist community, offering a foundation for potential interventions and educational initiatives.

CHAPTER 2 – PUBLICATION FOR LITERATURE REVIEW

At the time of this submission, this article is awaiting submission to the journal: Health SA Gesondheid, and is formatted for the journal

A recommendation for the use of probiotics in community pharmacies in South Africa

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Abstract

Background:

There has been a substantial increase in the consumption of probiotics in the last decade in South Africa and it is expected that the demand for probiotics will increase. Probiotic supplements are available in community pharmacies in South Africa and the scope of practice of a pharmacist extends to having adequate knowledge and evidence-based information to provide advice on the use of probiotic supplements to patients. However, there are currently no

standard guidelines or documents for the use of probiotics in community pharmacies available for pharmacists in South Africa.

Aim:
This review aims to provide the pharmacy community with recommendations to inform evidence-based selection of probiotics in community pharmacies in South Africa.

Methods:
The authors referenced the article by Shekelle *et al.* (1999) for developing a recommendation regarding the minimum requirements for community pharmacists in the selection and counselling on probiotics.

Results:
There was limited information available for the use of probiotics in community pharmacies in South Africa, thereby this review has compiled recommendations that include relevant information to inform the selection and counselling of community pharmacists on the use of probiotics when dispensing probiotics.

Conclusion:
This review provides recommendations regarding the minimum requirements for community pharmacists in the selection and counselling on probiotics in pharmacies. The recommendation encompasses evidence-based selection and counselling criteria specifically designed for community pharmacists in South Africa. This recommendation equips community pharmacists in South Africa to support patients in making decisions regarding the appropriate use of probiotics within their designated scope of practice.

Contributions:
This review serves to offer recommendations for the use of probiotics in a pharmacy setting.

Keywords: probiotics, recommendation, safety, clinical indications, pharmacist

1. Introduction

Among the various supplements available on the market, probiotics have gained substantial popularity and widespread usage (Research and Markets, 2022). According to the probiotics market analysis report, the worldwide probiotics market was estimated to be worth 58.17 billion USD in 2021 and is expected to grow at a rate of 7.5% by 2030 (Grand View Research, n.d.). There was also a substantial increase in the consumption of probiotics in the last decade in South Africa and the demand for probiotics is expected to increase following the increased use of dietary supplements in Africa as well as the entry of major probiotic companies into the South African market (Research and Markets, 2022). The benefits of probiotics and their relevance to different populations are attracting the attention of healthcare professionals (Hammerman *et al.*, 2006, van den Nieuwboer *et al.*, 2014).

Probiotics are defined as living micro-organisms that positively affect the bowel micro-ecology and health conditions (Fuller, 1991). These beneficial effects are achieved through multiple mechanisms, including strengthening the mucosal barrier, competing for adhesion sites, and conferring an immunomodulatory effect on the host (Papastergiou *et al.*, 2014). Probiotics can also be used to alleviate the symptoms of adverse effects resulting from pharmacological treatments of certain health conditions. For example, when used as an adjunctive therapy with antibiotics in the treatment of *H. pylori* infections, probiotics increase tolerability and reduce adverse effects in humans, particularly nausea, taste disturbance, diarrhoea, and epigastric pain (Armuzzi *et al.*, 2001, Cremonini *et al.*, 2002, Nista *et al.*, 2004). Furthermore, a prospective study demonstrated that *Lactobacillus*, especially *Lactobacillus rhamnosus* GG, effectively reduces the frequency of severe diarrhoea and alleviates abdominal discomfort in patients diagnosed with colorectal cancer undergoing 5-Fluorouracil chemotherapy (Österlund *et al.*, 2007). However, it is essential to acknowledge that, as probiotics are gaining popularity worldwide, several concerns have been raised over the use of probiotics. One significant concern is the potential presence of antibiotic-resistance genes within probiotics (Imperial and Ibana, 2016).

The current available international guidelines, including the Evaluation of Health and Nutritional Properties of Probiotics in Food from the Joint Food and Agriculture Organisation of the United Nations and the World Health Organisation (FAO/WHO) Expert Consultation and Probiotics and Prebiotics Guidelines from the World Gastroenterology Organisation

(WGO) (Doron and Snydman, 2015, Kothari *et al.*, 2019, Sharma *et al.*, 2019, Guarner *et al.*, 2023), mention the safety considerations on antibiotic resistance relating to probiotic supplements, however, these guidelines do not offer the standards for time periods during which probiotic supplements should be taken, the required number of Colony Forming Units, and the number of bacterial strains that may be contained in probiotic supplements. The joint FAO/WHO Expert Consultation believes that a set of principles and practical criteria must be used to generate guidelines to prove the safety of probiotics (FAO and WHO, 2002). Evidently, the comprehensive literature with broader context required for probiotic selection and counselling in the pharmacy setting remain unaddressed, and hence, this review aims to fill this crucial gap and provide South African pharmacists with a comprehensive recommendation on the use of probiotics based on available evidence. This recommendation aims to serve as a foundational resource, which can potentially form the basis for developing guidelines on the use of probiotics once additional research on probiotic use in South Africa is conducted.

The Good Pharmacy Practice South Africa (GPPSA) states that a pharmacist's first concern must be the welfare of the patient (SAPC, 2017). Despite probiotics not being regulated by South African Health Products Regulatory Authority (SAPRHA), the scope of a pharmacist extends to having adequate knowledge and evidence-based information to provide probiotic supplements to patients as probiotic supplements are available in community pharmacies in South Africa. Pharmacists have broad access to patient populations, and they should be able to counsel on the appropriate selection and counselling of probiotics (SAPC, 2017). However, there is limited correlation among the studies to provide informed decision-making regarding the use of probiotics for prevalent health conditions (Marcotte *et al.*, 2019, Happel *et al.*, 2020). Additionally, a study evaluating the probiotics market in South Africa concluded that an evaluation system should be implemented to safeguard consumers by identifying probiotics with standardized qualifications (Elliott and Teversham, 2004). Evidently, there is an urgent need for a reviewed document on appropriate selection based on minimum criteria and counselling for probiotics. Thus, this review aims to provide the pharmacy community with a recommendation to inform evidence-based selection of probiotics in community pharmacies in South Africa.

2. Methods

The methods of guideline development were used in the article by Shekelle *et al*. (1999) to develop a recommendation. The steps included identifying and refining the subject area, convening and assessing the evidence about the clinical question or condition to produce the resulting recommendation, translating the evidence into a recommendation, and including an external reviewer experienced in the relevant field.

The defining of the subject area included defining probiotics and the use of probiotics. The subject areas included identifying the minimum requirements for a probiotic, such as the number of strains and the number of Colony Forming Units, identifying the probiotics contributing to resistance, collating the benefits and concerns on the use of probiotics, and current probiotic guidelines, and identifying counselling recommendations for pharmacists. The final subject area was refining the use of probiotics that is relevant to community pharmacists. The main limitation of this review is that there are currently no official standards for probiotics and no regulations exist for probiotics in South Africa.

3. Review findings

Probiotics definition

Probiotics are defined as living micro-organisms that positively affect the bowel micro-ecology and health conditions (Fuller, 1991). The term "probiotic" is often misused as a synonym for beneficial members of commensal micro-organisms; however, the term "probiotic" is only used for products that contain an adequate dose of live micro-organisms that have been studied in target-host studies to confer a health benefit (Sanders, 2008). Most probiotic supplements contain Gram-positive bacteria, with *Lactobacillus* spp. and *Bifidobacterium* spp. being the most common species used therapeutically (Rodes et al., 2013).

Benefits of probiotics

Various health benefits are thought to be associated with the use of probiotics (FAO and WHO, 2002). Probiotics may be used in the management of patients experiencing acute diarrhoea and can be used for radiation-induced diarrhoea as well as antibiotic-associated diarrhoea (Fuccio *et al.*, 2009, Allen *et al.*, 2011). Probiotics also offer promising efficacy for the treatment of inflammatory diseases and irritable bowel syndrome (Dai *et al.*, 2013, Yoon *et al.*, 2014, Didari

et al., 2015, Cayzeele-Decherf *et al.*, 2017, Dale *et al.*, 2019), and probiotics show beneficial use as one of the alternative regimens to reduce the adverse effects of antibiotics used in *H. pylori* treatment (Lesbros-Pantoflickova *et al.*, 2007, Patel *et al.*, 2014, Enany and Abdalla, 2015). Furthermore, probiotics have been found to be beneficial to patients with hepatic encephalopathy due to the reducing effect of probiotics on plasma ammonia levels (Malaguarnera *et al.*, 2007, McGee *et al.*, 2011). It was also found that probiotics improve the health outcomes in patients at risk of cardiovascular disease by decreasing cardiovascular disease risk factors including high blood pressure, overweight Body Mass Index (BMI), high cholesterol and triglycerides, elevated HbA1c and serum glucose (Dixon *et al.*, 2020, Matsumoto, 2020, Olas, 2020).

Several international guidelines on probiotics provide current insights into their clinical applications. The joint FAO/WHO Expert Consultation provides guidance on the use of probiotics for various clinical conditions, including diarrhoea, *H. pylori* infections, inflammatory diseases and bowel syndromes, cancer, constipation, mucosal immunity, allergy, cardiovascular disease, and urogenital tract disorders (FAO and WHO, 2002). Additionally, probiotics guidelines from the WGO also provide probiotics recommendations for different clinical indications, such as diarrhoea, *H. pylori* infections, hepatic encephalopathy, Inflammatory Bowel Disease (IBD), colic, lactose malabsorption, necrotizing enterocolitis, liver diseases, and systemic infections (Guarner *et al.*, 2023). Guidelines, such as the American Gastroenterological Association (AGA) guideline, direct the application of probiotics for specific clinical purposes, such as managing diarrhoea induced by *H. pylori* infection treatment. Besides these international guidelines, numerous studies have researched the effectiveness of probiotics based on scientific evidence, and some examples are listed in Table 1.

Table 3: Effectiveness of probiotics for disorders

Disorders	Effectiveness	Probiotics	References
Diarrhoea	Probiotics have demonstrated the ability to reduce the duration of acute diarrhoea in adults and especially in children by approximately 24 hours. For instance, in a recent Cochrane review encompassing 63 studies, 56 of which involved infants and young children, a specific probiotic agent with or without oral rehydration therapy was compared with a placebo or no probiotic in individuals experiencing acute diaorrhoea. The findings revealed a statistically significant reduction in the duration of diarrhoea by 27.46 hours when probiotics were consumed by 4555 patients, especially with oral rehydration therapy. The authors concluded that *Lactobacillus rhamnosus* GG was identified as the most effective probiotic based on the studies available at the time of the analysis. Probiotics can also be considered as a preventive measure for radiation-induced diarrhoea and antibiotic-induced diarrhoea. In a placebo-controlled trial, it was observed that probiotics containing lactic acid-producing bacteria have been shown to provide protection against diarrhoea induced by postoperative radiation therapy in patients with sigmoid, rectal, or cervical cancer. The trial included 490 patients and spanned from the commencement	*Lactobacillus rhamnosus* GG*, L. plantarum* MP2026, *Lactobacillus acidophilus* CL1285 and *L. casei* LBC80R	(FAO and WHO, 2002, Huang *et al.*, 2002, Delia *et al.*, 2007, Pillai and Nelson, 2008, Fuccio *et al.*, 2009, Allen *et al.*, 2011, Hickson, 2011, Goldenberg *et al.*, 2017, Liu *et al.*, 2017, Hu *et al.*, 2021, Zhang *et al.*, 2022, Guarner *et al.*, 2023)

Disorders	Effectiveness	Probiotics	References
Diarrhoea	of radiation therapy to the completion of the scheduled cycles. Patients who received the placebo experienced more severe diarrhoea in comparison to the patients' receiving probiotics, with grade 3 or 4 diarrhoea documented in 55.4% of placebo-treated patients, as opposed to only 1.4% in the probiotics-treated patients. However, it must be noted that statistical significance was not achieved. The limited number of studies available on the use of probiotics for radiation-induced diarrhoea emphasizes the necessity for further research to determine strains that can maximize efficacy. In a systematic review by Pillai and Nelson (2008) assessing treatments for *Clostridium difficile*-associated diarrhoea, the authors found insufficient evidence to support the effectiveness of probiotic therapy as a supplementary treatment with antibiotics. However, this study can be compared with a more recent systematic review referenced by the World Gastroenterology Organisation guideline, which included 31 randomized controlled trials. The review by Goldenberg *et al*. (2017), compared probiotics treatment to placebo, alternative prophylaxis, or no treatment. The review included 31 randomised controlled trials involving 8672 patients. The review suggested that specific Lactobacillus probiotic strains, such as *Lactobacillus acidophilus* CL1285 and *L. casei* LBC80R, demonstrated a statistically		

Disorders	Effectiveness	Probiotics	References
	significant reduction of 60% in the risk of *Clostridium difficile*-associated diarrhoea among adults and children receiving antibiotic therapy.		
Inflammatory Bowel Diseases	Inflammatory Bowel Diseases (IBD) such as Ulcerative colitis and Crohn's disease are immunologically mediated disorders. Probiotics have the ability to modulate microflora which may lead to the remediation of inflammatory conditions. For example, guidelines from the World Gastroenterology Organisation suggest that probiotic strains such as *L. acidophilus, L. plantarum, L. casei, B. lactis, S. cerevisiae* may be safe and equally effective as conventional therapy for inducing remission in moderate ulcerative colitis. A clinical trial cited by the World Gastroenterology Organisation showed a significant remission of ulcerative colitis in 94% of patients in the sigmoidoscopy assessment when *Lactobacillus* and *Bifidobacterium* strains were orally consumed for six weeks in 32 patients with mild to moderate ulcerative colitis who did not respond to conventional therapy. However, this finding contrasts with a review by Kaur *et al*. (2020), which analysed 14 randomized controlled trials (865 randomised participants) to investigate the effectiveness of probiotics compared to standard treatments or placebo in the induction of remission of ulcerative colitis. The review concluded that the evidence supporting the induction of remission in mild to moderate ulcerative	*L. acidophilus, L. plantarum, L. casei, B. lactis, S. cerevisiae*	(Bibiloni *et al.*, 2005, Barclay *et al.*, 2007, Dai *et al.*, 2013, Yoon *et al.*, 2014, Didari *et al.*, 2015, Cayzeele-Decherf *et al.*, 2017, Dale *et al.*, 2019, Kaur *et al.*, 2020)

Disorders	Effectiveness	Probiotics	References
	colitis had a low level of certainty. Furthermore, the absence of evidence supporting the effectiveness of probiotics in more severe forms of ulcerative colitis emphasizes the need for additional studies. Given the chronic nature of IBD, including ulcerative colitis, further research is required to enhance the understanding and refine the application of probiotics.		
Helicobacter pylori Infection Associated Adverse Effects *Helicobacter pylori* Infection	*Helicobacter pylori* is one of the most prevalent infections worldwide and was identified as a high-priority bacterium by WHO 1994. *Helicobacter pylori* is the major risk factor for peptic ulcer disease and gastric cancer. Failure to treat *H. pylori* results from multiple factors, such as antibiotic resistance and patient noncompliance. As the incidence of treatment failure of *H. pylori* infections increases, some studies have focused on the use of probiotics as one of the alternative and complementary regimens to reduce the adverse effects of antibiotics used in *H. pylori* treatment. A systematic review, including 45 randomized controlled trials, revealed that the use of probiotics to supplement standard therapy in patients with *H. pylori* decreased the overall rate of adverse events significantly by approximately 41%, irrespective of patient age, dosage of probiotics, and therapy regimen in comparison to patients not consuming probiotics. This finding corresponds to a meta-analysis to assess the effect of multi-strain probiotics as adjunct	*L. casei, L. johnsonii* La1, *L. rhamnosus* GG	(Lee *et al.*, 1999, Michetti *et al.*, 1999, Duynhoven and Jonge, 2001, Lesbros-Pantoflickova *et al.*, 2007, Gotteland *et al.*, 2008, Patel *et al.*, 2014, Aiba *et al.*, 2015, Enany and Abdalla, 2015, McFarland *et al.*, 2015, Zhang *et al.*, 2015, Dore and Pes, 2021, Shah *et al.*, 2021)

Disorders	Effectiveness	Probiotics	References
Associated Adverse Effects	therapy for *H. pylori* eradication and prevention of adverse effects. The meta-analysis included 19 randomised controlled trials involving 2730 participants. The study stated that the limited availability of trials using the identical mixture of strains restricted the capacity to draw firm conclusions regarding a few strains included in the study. However, its findings revealed that the use of adjunct probiotics resulted in a statistically significant reduction of 14% in adverse events and 4.5% in antibiotic-associated diarrhoea when combined with triple therapy, compared to patients not consuming probiotics.		

Disorders	Effectiveness	Probiotics	References
Impaired Mucosal Immunity	Lactic Acid Bacteria (LAB), such as *Lactobacillus casei, Lactobacillus rhamnosus,* and *Lactobacillus plantarum,* enhances immunity of the gastrointestinal linings. The mechanisms of action by which probiotic strains affect the immune system in humans are not yet fully understood, however, it may the results of increased innate or acquired immune response, which induces a systemic and mucosal immune response. *In vitro* and animal studies suggest that probiotic strains can modify immune parameters, as referenced by the FAO/WHO guideline. For example, it was observed that orally administered probiotics containing lactic acid bacteria stimulate the gut immune cells to release inflammatory factors such as regulatory cytokines when administered to mice, which resulted in the gastrointestinal enhanced mucosal immunity. Another animal-model study suggested the ingestion of *L. rhamnosus* (HN001), *L. acidophilus* (HN017), or *B. lactis* (HN019) has the potential to improve various aspects of natural and acquired immunity in healthy mice. However, further studies on humans with larger sample sizes, a longer duration, and different probiotic strains are needed in order to evaluate the effect of probiotics on impaired mucosal immunity.	*L. casei, L. rhamnosus,* and *L. plantarum, L. acidophilus, B. bifidum* and *B. lactis*	(Gill *et al.*, 2000, Vitini *et al.*, 2000, FAO and WHO, 2002, Perdigon *et al.*, 2002, Galdeano and Perdigon, 2006, Szajewska *et al.*, 2014a)
Allergy	A limited number of studies have shown the effectiveness of probiotics in the prevention of allergic symptoms of atopic dermatitis and allergic asthma in	*L. rhamnosus, L.*	(Furrie, 2005, Niers *et al.*, 2009, Yeşilova *et al.*, 2012,

Disorders	Effectiveness	Probiotics	References
	infants. For instance, a placebo-controlled trial revealed that the prevalence of eczema decreased by 16.8% (p=0.035) during the first three months of life among infants with family history of allergic disease when freeze dried powder of the probiotic mixture of *B. bifidum* W23 *and B. lactis* W52 were consumed by 156 mothers and their infants for the first 12 months of the infants' lives, in comparison to the placebo group. This may be due to the strengthening of the mucosal barrier and preventing the circulation of undigested food proteins in the gastrointestinal tract, thereby preventing stimulation of the antigen-specific immune response. However, there are contradictory results on the effectiveness of probiotics in the prevention and treatment of certain allergies such as food allergies, allergic rhinitis and respiratory allergies. A systematic review and meta-analysis, which included 23 studies, concluded that while probiotics may be beneficial in improving symptoms of allergic rhinitis, the existing evidence is limited due to variations in study designs and outcome measures. Additional studies are necessary to determine the effectiveness of probiotics for allergies.	*fermentum, B. bifidum, B. lactis, L. acidophilus, L. casei, L. salivarius.*	Burks *et al.*, 2013, Kuitunen, 2013, Shi *et al.*, 2016, Adler-Neal *et al.*, 2019)
Hepatic Encephalopathy	Hepatic encephalopathy is a reversible condition characterized by impaired brain function, occurring in patients with advanced liver diseases. Plasma ammonia levels are increased in the case of hepatic encephalopathy and	*L. plantarum, L. casei, L. acidophilus, L.*	(Dhiman *et al.*, 2010, McGee *et al.*, 2011, Shukla *et al.*, 2011, Agrawal *et al.*,

Disorders	Effectiveness	Probiotics	References
	probiotics have been found to be beneficial to patients with hepatic encephalopathy due to the reducing effect of probiotics on plasma ammonia levels. However, despite recommendations in guidelines such as the WGO guideline, suggesting probiotics containing strains, including *L. plantarum, L. casei, L. acidophilus* for hepatic encephalopathy, various studies suggest the need for additional randomized clinical trials to further investigate their effectiveness. For instance, a Cochrane review, as cited in the WGO guideline, examined seven randomized trials that compared probiotics at various dosages with placebo or no intervention, or with other treatments in patients with hepatic encephalopathy. This review suggested that while probiotics appear to lower plasma ammonia concentration compared to placebo or no intervention, it cannot be conclusively stated that probiotics are effective in improving clinically relevant outcomes of hepatic encephalopathy.	*delbrueckii subsp. bulgaricus, B. infantis, B. longum, B. breve.*	2012, Zhao *et al.*, 2015, Ferenci, 2017, Guarner *et al.*, 2023)
Cardiovascular Diseases	Risk factors for cardiovascular disease include high blood pressure, elevated BMI, high levels of cholesterol and triglycerides, as well as increased HbA1c and serum glucose. The FAO/WHO guideline states that probiotics improve the health outcomes in patients at risk of cardiovascular disease by reducing these risk factors. For example, probiotic preparation containing bacterial	*L. plantarum*	(FAO and WHO, 2002, Ahrén *et al.*, 2015, Szulińska *et al.*, 2018, Dixon *et al.*, 2020, Lewis-Mikhael *et al.*, 2020,

Disorders	Effectiveness	Probiotics	References
	strains such as *Lactobacillus* and *Bifidobacterium* has been found to lower systolic blood pressure in obese postmenopausal women. The mechanisms by which probiotics influence patients with cardiovascular disease include a reduction in oxidative stress in cells, inflammation, cholesterol levels and blood pressure. However, despite the positive findings regarding the use of probiotics in the context of cardiovascular diseases, further human studies are required to ascertain the precise health benefits of probiotics on the cardiovascular system.		Matsumoto, 2020, Olas, 2020, Oniszczuk *et al.*, 2021, Lugito *et al.*, 2022, Tian *et al.*, 2023)
Urogenital Disorders Urogenital Disorders	Bacterial vaginosis is a urogenital disorder which often results from insufficient *Lactobacilli,* and it was demonstrated that oral probiotics lengthen remission in patients with bacterial vaginosis, and improve clinical and microbiological parameters. Furthermore, a review stated that most relevant clinical trials have suggested that oral administration of *L. acidophilus,* or *L. rhamnosus* GR-1, and *L. fermentum* RC-14 leads to an increase in the *Lactobacilli* in the vaginal area, when given over hundred-thousand Colony Forming Units (CFUs) for two months, can normalize the vaginal flora, assist in treating the infections, and prevent recurrence of vaginal bacteriosis. Urinary Tract Infections (UTIs) is another type of urogenital disorders and is a microbial infection in any part of the urinary	*L. rhamnosus* GR-1 *and L. reuteri* RC-14, *L. crispatus.*	(FAO and WHO, 2002, Reid *et al.*, 2003, Falagas *et al.*, 2006, Uehara *et al.*, 2006, Stapleton *et al.*, 2011, Grin *et al.*, 2013, Stepanova *et al.*, 2013, Heczko *et al.*, 2015, Kumar *et al.*, 2015, Butler *et al.*, 2016, Ziyadi *et al.*, 2016, Toh *et al.*, 2017, Ng *et al.*, 2018, Daniel *et al.*, 2020)

Disorders	Effectiveness	Probiotics	References
	tract including the kidneys, ureters, bladder, and urethra. Over several decades, the use of probiotics has been considered for the prevention of UTI and *L. rhamnosus* GR-1 and *L. reuteri* RC-14 are the most effective strains for the prevention of UTIs. However, despite the positive reports on the use of probiotics for urogenital disorders, probiotics do not meet the minimum criteria as alternative treatment of urogenital disorders and further research is required as there is still insufficient data about the preventative and treatment effects of probiotics in urogenital disorders.		

Safety considerations

Antibiotic resistance profiles of probiotics

The prolonged use of antibiotics has been associated with various drug-related issues, including specific adverse effects of drugs and the emergence of multidrug-resistant bacteria (Yang *et al.*, 2020). Resistance to antibiotics has become a global issue due to an increase in antibiotic consumption (Guevara and Cogdill, 2020). Ingestion of antibiotic resistance genes could influence the pharmacodynamics of antibiotics (Gueimonde *et al.*, 2013a) and certain probiotic strains have been found to transfer antibiotic resistance to human intestinal pathogens (European Food Safety Authority, 2008, Gueimonde *et al.*, 2013b). The FAO/WHO guidelines state that research is required to discover the potential for transmission of antibiotic resistance genetic elements of probiotics to other intestinal micro-organisms (FAO and WHO, 2002). Table 2 shows common probiotic strains which carry antimicrobial resistance. Although it is generally accepted that probiotics have good safety records, the transfer of antibiotic resistance genes raises safety concerns (Gueimonde *et al.*, 2013b). Thus, the bacteria in probiotics for humans should not contain any antibiotic-resistance genes (European Food Safety Authority, 2008).

In most cases, antibiotic resistance represents an intrinsic species or genus, which are not likely to be transferred and constitute any safety concern (Salminen *et al.*, 1998). However, it is crucial to consider safety implications associated with antibiotic resistance, particularly concerning plasmid-mediated resistance, which has the potential for transferring antibiotic resistance traits (Salminen *et al.*, 1998). Consequently, probiotic strains harbouring resistance plasmids should not be utilized for human or animal probiotic purposes as the utilization of antibiotics in human and animal treatment, along with the dissemination of antibiotic-resistant bacteria, can facilitate the acquisition and propagation of resistant genes (Salminen *et al.*, 1998). Only when a probiotic strain has been unequivocally identified, characterized, thoroughly screened, and its mechanisms of action have been scientifically elucidated, can it be accurately labelled (Donohue, 2006). A comprehensive risk-benefit assessment of probiotics in comparison to existing treatments is vital to provide high-quality evidence to the use of probiotics in patients.

Table 4: Common probiotic strains which carry antimicrobial resistance

Resistance strains	Antibiotics found to be resistant	Acquisition	Transferability	Safety Implication	Reference
L. acidophilus BFE 7444	Ciprofloxacin, Gentamycin, Streptomycin	Intrinsic	Non-transferable	Antibiotic resistance determinants are not likely to be present or can be transferred, thus the strains are safe for human consumption.	(Hummel *et al.*, 2007, Ashraf and Shah, 2011)
L. rhamnosus GG	Cloxacillin, Fusidic acid, Gentamycin, Kanamycin, Nalidixic acid, Neomycin, Polymyxin, Streptomycin, Vancomycin	Intrinsic	Transferable	Antibiotic resistance determinants are likely to be transferred or spread. The safety of the strains should be determined by testing the presence of transferable resistance gene before being used as probiotics.	(Tynkkynen *et al.*, 1998, Zhou *et al.*, 2005, Ashraf and Shah, 2011)
L. casei BFE 7445	Ciprofloxacin, Gentamycin, Streptomycin	Intrinsic	Non-transferable	Antibiotic resistance determinants are not likely to be present or can be transferred, thus the strains are safe for human consumption.	(Hummel *et al.*, 2007, Ashraf and Shah, 2011, Shao *et al.*, 2015)
L. reuteri SD 2112 (ATCC 55730)	Clindamycin, Cefotaxime, Fusidic acid, Kanamycin, Lincomycin, Methicillin, Nalidixic acid, Nitrofurantoin, Ofloxacin, Oxacillin, Penicillin, Streptomycin, Tetracycline, Tobramycin, Vancomycin	Plasmid borne	Transferable	Antibiotic resistance determinants are likely to be transferred or spread. The safety of the strains should be determined by testing the presence of transferable resistance gene before being used as probiotics.	(Kastner *et al.*, 2006, Egervärn *et al.*, 2009, Szajewska *et al.*, 2014b)
L.plantarum 423	Amoxicillin, Cefadroxil, Roxithromycin, Doxycycline	Intrinsic	Non-transferable	Antibiotic resistance determinants are not likely to be present or can be transferred, thus the strains are safe for human consumption.	(Botes *et al.*, 2008a, Botes *et al.*, 2008b, Van Zyl *et al.*, 2019)
B. lactis DSM 10140	Gentamycin, Kanamycin, Nalidixic acid, Ofloxacin, Streptomycin, Tetracycline	Plasmid borne	Transferable	Antibiotic resistance determinants are likely to be transferred or spread. The safety of the strains should be determined by testing the presence of transferable resistance gene before being used as probiotics.	(Zhou *et al.*, 2005, Kastner *et al.*, 2006, Sanders, 2006, Ashraf and Shah, 2011)

Resistance strains	Antibiotics found to be resistant	Acquisition	Transferability	Safety Implication	Reference
B. lactis HN049	Cloxacillin, Gentamycin, Kanamycin, Nalidixic acid, Neomycin, Polymyxin, Streptomycin	Intrinsic	Non-transferable	It was tested to prove that the strains do not contain clinically significant transmissible antibiotic resistance genes, thus the strains are safe for human consumption.	(Zhou *et al.*, 2005, Ashraf and Shah, 2011)
B. breve rpsL	Streptomycin	Atypical	Non-transferable	Chromosomal mutation of the rpsL gene for ribosomal protein S12 cause resistance so it is unlikely to be transferred to another microorganism.	(Kiwaki and Sato, 2009, Sato and Iino, 2010, Ashraf and Shah, 2011, Gueimonde *et al.*, 2013b)
Enterococcus mundtii (ST4SA)	Ciprofloxacin, Amoxicillin, Roxithromycin, Doxycycline	Intrinsic	Transferable	Antibiotic resistance determinants are likely to be transferred or spread. The safety of the strains should be determined by testing the presence of transferable resistance gene before being used as probiotics.	(Murray, 1990, Botes *et al.*, 2008a, Botes *et al.*, 2008b, Ben Braïek and Smaoui, 2019)
Bacillus clausii SIN	Chloramphenicol, Cephalosporins, Gentamycin, Streptomycin	Atypical	Non-transferable	Antibiotic resistance determinants are not likely to be present or can be transferred, thus the strains are safe for human consumption.	(Bozdogan *et al.*, 2004, Galopin *et al.*, 2009, Abbrescia *et al.*, 2014, Lahiri *et al.*, 2022)

Critically ill patients

There are limited studies on the use of probiotics for critically ill patients. An example is a systematic review and meta-analysis, which included 30 randomized controlled trials to assess clinical outcomes in critically ill patients associated with probiotic therapy, either alone or in combination with prebiotic fibre. This review revealed a significant reduction in the incidence of ventilator-associated pneumonia (Manzanares *et al.*, 2016). However, there is currently insufficient evidence supporting the routine use of probiotics for critically ill patient (Naseri *et al.*, 2022). It is also important to note that the majority of studies emphasize short-term beneficial effects and do not extensively address long-term safety concerns (Yazdankhah *et al.*, 2009). Hence, it is not recommended to utilize probiotics in such patient populations due to the associated risks and potential for worsening their health status.

Immunological considerations

Micro-organisms induce effects on the human immune system, where the indigenous intestinal micro-organisms are essential to develop and maintain immune homeostasis (O'Hara and Shanahan, 2006). The immune stimulation effects of probiotics are known to be especially beneficial in healthy people with compromised immune function (Sanders *et al.*, 2010). This includes people that are stressed, aged, young, and pregnant. Although the immunocompromised group of people may also benefit from probiotics, they might be at higher risk for adverse effects, such as inducing septic conditions (Sanders *et al.*, 2010). This happens when probiotic strains, such as *L. reuteri* SD 2112*,* that carry virulence factors or antibiotic resistance genes reduce the capability for microbial clearance, and facilitate translocation or facilitate infections themselves (Sanders *et al.*, 2010). Whether probiotics will produce immune-stimulating or immune-suppressing effects on the patient depends on the microbial signals, genetic factors of the patient and environmental triggers; therefore, the specific probiotic structure-function relationships in specific populations should be characterised to decrease detrimental effects in the patient (Sanders *et al.*, 2010).

Infants

The significant role of the microbiota on the development of the gut-associated immune system is prompting clinical investigations into the application of probiotics in infant formula (Sanders *et al.*, 2010). While certain studies, including a review of ten studies on probiotics, concluded that there was no significant impact on growth, stool frequency, or consistency, the use of

probiotics is generally considered safe and well-tolerated in normal, healthy infants, as supported by clinical practice (Sanders *et al.*, 2010, Mugambi *et al.*, 2012). A study on the use of probiotics in infants showed that the administration of infant formulas containing *Bifidobacterium lactis* was well tolerated, resulting in a reduced incidence of gastrointestinal irritability, as well as assisting in growth of the infants (Saavedra *et al.*, 2004).

In clinical practice, infant formulas containing *Lactobacillus, Bifidobacterium*, and/or *S. thermophilus* are currently permitted in certain regions of Asia, Europe, and the United States (Sanders *et al.*, 2010). Although there are several infant formulas containing probiotics in South Africa, it is essential to consider that some of them contain *L. reuteri*, which is mentioned in the table 2 as having transferable antibiotic resistance genes. The CFUs of probiotic strains in the infant formulas must also be considered to ensure that infants consume an adequate number of probiotics for potential health benefits. Long-term effects have only rarely been measured and thus further research on the immunological effects of probiotics and the long-term effects of probiotics on infants should be conducted, since infants are vulnerable to immune system dynamics.

Children, pregnancy, lactation

Research has demonstrated that the consumption of probiotics, particularly during lactation, yields beneficial effects on the gut microbiota of newborns, particularly those delivered via Caesarean section (Martín-Peláez *et al.*, 2022). This is mainly due to the alterations in the maternal gut and breastmilk microbiota which have been observed after changes in maternal diet to include probiotics during pregnancy and lactation (Zaidi *et al.*, 2021). This resulted in positive alterations in the infant gut microbiota, with more pronounced effects observed in breastfed infants as opposed to those fed with formula (Zaidi *et al.*, 2021). The intake of probiotics also showed positive effects in children when probiotics were directly consumed (Agustina *et al.*, 2013, Onubi *et al.*, 2015). For example, dietary intake of probiotics showed beneficial effects in children, especially in undernourished children in terms of weight and height (Agustina *et al.*, 2013, Onubi *et al.*, 2015).

4. Implications and recommendations

Minimum requirements

It is recommended that probiotics meeting the minimum requirements are used by pharmacists. Several studies of probiotic characteristics, selection criteria, and their role in human health provides selection criteria for probiotics for producing beneficial effects (Naidu *et al.*, 2012, Draper *et al.*, 2016, Gupta *et al.*, 2018). The minimum requirements of probiotics are shown in the list below.

A list of minimum requirements of probiotics

- Be of human origin (Plaza-Diaz et al., 2019)
- Multiple-strains consisting of at least three different strains (Giri et al., 2014, Hao et al., 2014, Kuebutornye et al., 2020)
- At least 10^9 Colony Forming Units (CFUs) should be consumed daily (Johnston et al., 2006, Minelli and Benini, 2008, Kechagia et al., 2013)
- Be able to modulate immune responses in the host; be able to survive and show resistance to enzymes in the gastrointestinal tract (Gupta *et al.*, 2018)
- Exhibit antagonism against pathogens; include microbes that are alive in an adequate number when administered; and include strains that are identified genetically, classified, and designated by using the latest terminology (Hill *et al.*, 2014)
- Provide benefits to the host by growing and exerting activity in the human body (Salminen *et al.*, 1998, Morelli, 2000)
- Should preferably not have a micro-organism that is able to transfer antimicrobial resistance (European Food Safety Authority, 2008)

Common side effects of probiotics

It is recommended that pharmacists provide specific information during counselling regarding the common side effects associated with probiotics. While probiotics are generally recognized as safe, it is important to note that a few side effects have been associated with their use. The most common side effects of probiotics are related to gastrointestinal disturbances, including bloating, diarrhoea, nausea, flatulence, dyspepsia, and abdominal pain, typically resolving themselves within a few days or weeks after starting probiotic intake (Cleveland Clinic, 2020).

More severe side effects include respiratory infections, abscesses, allergic reactions, and medical conditions like sepsis, *Saccharomyces cerevisiae* fungemia and endocarditis (Katkowska *et al.*, 2021). As probiotics are readily available over the counter, patients may have limited opportunities to seek counselling from pharmacists regarding potential side effects. Therefore, it is recommended for pharmacists to take proactive measures in informing patients about these potential side effects and offer appropriate counselling to ensure their well-being and safety.

How to use probiotics

Optimal duration for probiotic consumption

While the evidence regarding the optimal use of probiotics varies, it is generally acknowledged that probiotics provide the greatest health benefits when used according to the manufacturer's recommendations (FAO and WHO, 2002, Roobab et al., 2020). Notably, probiotics have been shown to be most effective when administered approximately 30 minutes prior to a meal on an empty stomach (Tompkins et al., 2011). Determining the optimal duration for probiotic consumption to attain beneficial effects for specific health conditions can be challenging, mainly due to the limited evidence in studies regarding the recommended timeframe for taking probiotics. However, there are studies that suggest an optimal duration for probiotic consumption to achieve beneficial effects. For example, a randomized clinical trial demonstrated a reduced overall risk of diarrhoea in children when taking multi-strain probiotics, including *B. bifidum* W23, *B. lactis* W51, and *L. acidophilus* W37, during the consumption of antibiotics continued to one week after the completion of the course (Lukasik *et al.*, 2022). While studies may provide some guidance on the use of probiotics, additional research is required to establish more precise recommendations on how to use probiotics.

Benefits, risks, and recommendations in clinical practice

There are varying degrees of evidence regarding the health benefits exerted by probiotics. However, for pharmacists to recommend a probiotic for specific health conditions, it is essential that benefits of using probiotics significantly outweigh the associated risks. Safety considerations associated with probiotics must be taken into account when providing probiotics to patients. The evidence sufficiently supports the effectiveness of probiotics alongside rehydration therapy in managing acute, infectious diarrhoea and diarrhoea induced by antibiotics, including instances related to the use of antibiotics for *H. pylori* treatment (Armuzzi

et al., 2001, Cremonini *et al.*, 2002, Nista *et al.*, 2004). However, the available data collectively provide limited guidance on the optimal timing, formulation, dosage, duration, and appropriate patient selection of probiotics. For instance, specific probiotic strains contained in probiotic supplements have been discovered to transfer antibiotic resistance to human intestinal pathogens. *Enterococcus mundtii* (ST4SA) has exhibited resistance to amoxicillin, a component of the triple therapy used for *H. pylori* infection (Botes *et al.*, 2008b). As a result, *Enterococcus mundtii* (ST4SA) should not be recommended by pharmacists as an adjunct therapy to antibiotic treatment for *H. pylori* infection. Consequently, the use of probiotics in conjunction with *H. pylori* requires further investigation to refine their application in clinical settings.

Another crucial consideration when providing probiotics is the inclusion of certain probiotics in infant formulas. While numerous infant formulas in South Africa incorporate probiotics, it should be noted that some formulations contain *L. reuteri*, a strain which has been studied to possess transferable antibiotic resistance genes (Kastner *et al.*, 2006, Egervärn *et al.*, 2009, Szajewska *et al.*, 2014b). Evaluating long-term effects of specific probiotic strains, particularly regarding the immunological impact and extended implications on infants is crucial considering infants are vulnerable to immune system dynamics. Consuming the adequate number of CFUs of probiotic strains in these formulas is essential to ensure infants receive an adequate quantity of probiotics for potential health benefits. Therefore, it is strongly recommended that pharmacists thoroughly assess probiotics before recommending them to patients.

Probiotics, such as *Lactobacillus casei, Lactobacillus rhamnosus,* and *Lactobacillus plantarum,* play a role in enhancing the immunity of the gastrointestinal linings. However, individuals within the immunocompromised population may face an elevated risk of experiencing adverse effects, potentially leading to rare instances of septic conditions (Sanders *et al.*, 2010). Whether probiotics will produce immune-stimulating or immune-suppressing effects on the patient depends on the microbial signals, genetic factors of the patient and environmental triggers. Therefore, further studies involving larger sample sizes, extended durations, and various probiotic strains in human subjects are recommended to assess the effects of probiotics on impaired mucosal immunity. It is also crucial to characterize specific probiotic structure

function relationships in distinct populations to minimize potential adverse effects in patients (Sanders *et al.*, 2010).

Numerous clinical trials and experimental studies have demonstrated the efficacy of *Saccromyoces boulardii* as a promising biotherapeutic agent for the prevention and treatment of various gastrointestinal diseases (McFarland, 2010, Kelesidis and Pothoulakis, 2012, Feizizadeh *et al.*, 2014). However, nearly 100 cases of *S. boulardii*-associated fungemia have been reported (Vandenplas *et al.*, 2009). The source of the fungemia is believed to from either translocation within the digestive tract or contamination of the central venous line by the colonized hands of healthcare workers (Hennequin *et al.*, 2000). Careful evaluation of the potential benefits of *S. boulardii* is crucial when recommending probiotics containing *S. boulardii* to patients. Caution is warranted, especially in patients with predisposing risk factors, such as immunocompromised patients. To explore potential therapeutic applications, larger prospective placebo-controlled clinical trials are imperative.

Limitations of probiotic use in health conditions

Currently, it is not recommended to use probiotics for health conditions such as IBD, impaired mucosal immunity, allergy, hepatic encephalopathy, urogenital disorders, and cardiovascular disease as there is insufficient evidence for pharmacists to provide patients with evidence-based recommendations regarding the use of probiotics. Evidence for use of probiotics in an outpatient setting is limited mainly to the management of diarrhoea due to infection or as a result of side effects due to antibiotic consumption. Conducting a comprehensive risk-benefit assessment of probiotics in comparison to existing treatments is crucial to provide high-quality evidence to the use of probiotics in patients. Therefore, the benefits of probiotics would be evident when robust efficacy data from statistically significant human studies are available.

Regulatory framework in probiotic products

Probiotics are classified as category D health supplements according to the General Regulations outlined in the Medicines and Related Substances Act of 1965 (Act 101 of 1965) in South Africa (SAHPRA, 2022). The Complementary Medicines – Health Supplements Safety and Efficacy guideline issued by SAHPRA offers recommendations for applicants seeking to register health supplements. It reflects SAHPRA's current perspective on the quality,

safety, and efficacy of these medicines. In this guideline, specific probiotic strains are listed with a minimum daily level requirement of more than a billion CFUs per dosage unit. Additionally, the guideline provides health supplement claim specifications for probiotics. SAHPRA states that products falling within this category of Complementary Medicines must contain only the substances stated on the label, not include any human-derived substances, omit substances deemed undesirable by the Authority, exclude scheduled substances listed as Schedule 1 or higher (if indicated for any listed purposes in the schedule), and not be in injectable form. Probiotics are expected to adhere to these guidelines to ensure compliance and safety.

The application of good manufacturing practices with quality assurance is recommended. It is crucial to ensure clear labeling for probiotics available in the market, which should include information on minimum dosage recommendations and verifiable health claims. This will provide consumers with transparent and accurate information about the appropriate dosage and the specific health benefits associated with the product.

It is recommended to establish a regulatory framework to address various aspects related to probiotics, including efficacy, safety, labeling, fraud, and claims. Probiotic products that have demonstrated defined health benefits should be allowed to describe these specific benefits. It is recommended that surveillance systems, such as post-marketing surveillance, are established to record and analyse any adverse events associated with probiotics. These systems can also be utilized to monitor the long-term health advantages of specific probiotic strains. Efforts should be made to increase the availability of probiotic products, particularly for vulnerable populations at high risk of morbidity and mortality. Further research is required to address the criteria and methodologies for probiotic selection and evaluation.

5. Conclusion

This review provides a recommendation for the criteria to be considered when selecting and counselling on the use of probiotics. As there is a substantial increase in the consumption of probiotics in South Africa, pharmacists will be approached more frequently by patients regarding the use of probiotics. Based on the findings of this review, pharmacists should be equipped with adequate knowledge and evidence-based information when recommending the

use of probiotic supplements to patients. Evidence-based selection and counselling criteria for the use of probiotics has been presented, to guide community pharmacists in South Africa on the use of probiotics within the relevant scope of practice.

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The initial concept and draft of the article were developed by Ané Orchard, Razeeya Khan, and Muhammed Vally. Yedam Kim undertook the data collection. Data analysis was undertaken by Yedam Kim and Ane' Orchard. Yedam Kim drafted the original article, and Ané Orchard, Razeeya Khan, and Muhammed Vally reviewed the article. Mapitsi Thantsha acted as the critical reader and expert to review the guide, and also contributed towards the drafting of the article.

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Data availability
The sharing of data is not applicable to this article since no new data was generated or analysed in the course of this article.

Disclaimer:

The authors declare that the perspectives presented in the submitted article are their own and do not represent the official stance of the institution or funding entity.

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CHAPTER 3 – PUBLICATION FOR RESULTS

At the time of this submission, this article is awaiting submission to the journal: Health SA Gesondheid and is formatted for the journal

Use of probiotics in community pharmacy in South Africa: a survey of pharmacist attitudes, perceptions and knowledge

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Abstract

Probiotics are defined as living micro-organisms that exert a positive effect on the bowel micro-ecology and health conditions. There has been a substantial increase in the consumption of probiotics in the last decade in South Africa. Pharmacists, as experts in the field of medicine, play a crucial role in educating both patients and other healthcare professionals about the use of probiotics in the healthcare setting, however, the current state of pharmacist knowledge, attitudes and perceptions regarding probiotic supplements has not yet been examined in South Africa. Consequently, this study aims to assess pharmacist knowledge, attitudes and perceptions regarding probiotics. Of the 476 study respondents, only 237 respondents (49.8%) were included in the final analysis, as 239 surveys were incomplete. Among the respondents, 18.5% demonstrated a good level of knowledge about probiotics, while 11.3% demonstrated a

poor level of knowledge (Mean ± SD =13.81 ± 2.8). Half of the respondents (51.3%) displayed positive attitudes toward probiotics. Less than half of the respondents (47.6%) of the respondents displayed positive perceptions of probiotics. There was a statistically significant but weak correlation between the knowledge-attitudes variables (r = 0.1537, p = 0.0179) and attitude-perceptions variables (r = 0.3214, p = 0.0000). The study emphasizes the complexity of factors influencing individuals' knowledge, attitudes and perceptions regarding probiotics.

Keywords: probiotics, pharmacists, knowledge, attitudes, perceptions, colony forming units, strains, immunomodulatory, percentage, relationship, micro-organisms

1. Introduction

Following the global trend in the last decade, there was a substantial increase in the consumption of probiotics in South Africa and the demand for probiotics is expected to expand following the increased dietary supplement usage in Africa as well as the entry of major probiotic companies into the South African market (Research and Markets, 2022). The benefits of probiotics and their relevance to different populations are attracting the attention of healthcare professionals (Hammerman *et al.*, 2006, van den Nieuwboer *et al.*, 2014).

Pharmacists, as experts in the field of medicine, play a crucial role in educating both patients and other healthcare professionals on the use of probiotics in the healthcare setting (Amarauche, 2015b). Moreover, pharmacists are entrusted with the responsibility of supplying products following evidence-based decision-making principles (SAPC, 2017). There have been several international studies focused on the use of probiotics by pharmacists, and these studies concluded that that it is crucial for health practitioners, including pharmacists, to provide scientifically validated recommendations on the selection of probiotics (Amarauche, 2015a, Soni *et al.*, 2018a, Fijan *et al.*, 2019, Al-Qysi *et al.*, 2020). However, the attitudes, perceptions and knowledge of pharmacists regarding probiotic supplements has not yet been examined in South Africa. Consequently, this study aimed to assess pharmacist perceptions, attitudes, and knowledge regarding probiotics. Additionally, it aimed to investigate the rationale behind the selection and recommendation of probiotic supplements by pharmacists, the formal education received on the use of probiotics, and the pharmacist's understanding of the associated risks and benefits related to the use of probiotics.

2. Methodology

2.1 Study Design

A cross-sectional, descriptive study was conducted with community pharmacists across South Africa from January 2023 to September 2023.

2.2 Sample size

There are 3845 community pharmacies registered across South Africa. Each pharmacy is mandated to have a minimum of one pharmacist according to the Pharmacy Act, 1974 (Pharmacy Act, 1974). The sample size was equated as 350 participants, calculated using the Cochrane formula, taking into account the population size of 3845 community pharmacies and allowing for a margin of error of 5% and a confidence level of 95%. The estimated survey response rate is 60% of the designated sample size, comprising 231 pharmacists.

2.3 Data Collection

This survey encompassed eight demographic questions, which included biological sex, gender, age, geographic location, and education. The remaining questions related to knowledge (comprising 16 Yes/No questions and 3 Multiple Choice questions), attitudes (consisting of 5 Likert-like questions, 6 Yes/No questions, and 1 multiple choice question), and perceptions (involving 8 Likert-like questions). These questions were selected from previous surveys among healthcare professionals concerning the use of probiotics (Amarauche, 2015; Soni et al, 2018). The questions were validated through institutional ethics review and peer evaluation.

A link to the survey was distributed to community pharmacists via email using data from The South African Pharmacy Council (SAPC). The link was also shared within South African pharmacy social media groups, including Facebook and LinkedIn. Data collection was facilitated through the use of REDCap version 13.11.4. The survey was conducted with strict adherence to principles of confidentiality and anonymity. Individual identities were not collected, and the results of the study contain no personally identifiable information. Access to the data is limited solely to the researcher and supervisors.

2.4 Data analysis

Data were analysed quantitatively using descriptive statistical analysis and inferential statistics. The electronic data was analysed using statistical software (STATA SE 17.0). Numerical variables were presented as mean ± SD, and categorical variables were presented as percentages (%). The level of knowledge was categorized into three groups: good, fair, and poor: good if the respondent's total score was 75% or more, fair if 50–75%, and poor if less than 50% of the maximum score. Attitude scores were categorized as positive if the total score was greater than or equal to the mean score and negative if it was below the mean score. Perception scores were categorized as positive if the total score was greater than or equal to the mean score and negative if it was below the mean score. A Chi squared test was used to test the statistical differences among demographics and knowledge, attitudes and perceptions. Spearman's rank correlation coefficient was used to analyse the relationship between attitudes, perceptions and knowledge. In all tests, a $p < 0.05$ was considered statistically significant.

3. Results

3.1 Demographic characteristics of participants

Of the 476 study respondents, only 237 (49.8%) were included in the final analysis, as 239 surveys were incomplete. The respondents were from eight provinces, namely Eastern Cape, Free state, Gauteng, KwaZulu-Natal, Limpopo, Mpumalanga, North-West, and Western Cape. Most respondents (71.7%) were female. More than one third (40.9%) were between 21-30 years old and 34.2% were between 31-40 years old. The highest number of the respondents (78.1%) attained education up to the Bachelor of Pharmacy degree level, with more than half (57.8%) graduating with a Bachelor of Pharmacy degree in 2021 or later. None of the respondents graduated with a Bachelor of Pharmacy degree before 1960, and only 0.8% graduated between 1960-1970. The distribution of graduates was highest from the University 1 (21.9%). A comprehensive overview of the demographic characteristics of the respondents is presented in Table 1, designed with reference to the study by Arshad *et al*. (2021).

3.2 Knowledge of probiotics

Table 2 depicts the knowledge levels of the respondents regarding the use of probiotics. Among the respondents, 18.5% demonstrated a good level of knowledge about probiotics, while 11.3% demonstrated a poor level of knowledge (Mean ± SD = 13.81 ± 2.8). A large percentage of the

respondents were aware (88.6%) that not all bacteria cause infections. Most of the respondents (83.5%) defined probiotics correctly by recognizing that probiotics contain live micro-organisms (Table 3), however, a small percentage answered that probiotics contain dead micro-organisms (17.7%), herbs (10.1%) and synthetic medicine (14.3%). Regarding the benefits of probiotics, 83.5% of the respondents knew that probiotics alter the intestinal microbiota and confer an immunomodulatory effect (66.2%). The majority of the respondents (70.9%) were aware that probiotics are effective as an adjuvant in *Helicobacter pylori* infection (Table 3).

In terms of the potential for probiotics to carry antimicrobial resistant genes, 71.5 % were not aware of this possibility, and 73.4% of the respondents answered that there is a benefit to probiotics being resistant to antimicrobials as indicated in Table 3. When considering potential side effects of probiotics, most respondents (67.9%) were unaware that symptoms such as bloating, constipation and diarrhoea could be side effects of probiotics use. In terms of the respondents' knowledge of the minimum number of strains that should be contained in a probiotic supplement (Figure 1), the highest number of respondents indicated 'more than five strains' (27.4%), followed by 'two strains' (13.5%). Only 5.1% of the respondents answered 'three strains' and a small number of respondents (9.7%) answered that the number of strains that should be contained in a probiotic supplement was not important. Regarding the minimum number of Colony Forming Units (CFUs) that should be contained in a probiotic supplement (Figure 1), 33.3% of the respondents stated that there should be the minimum number of billion CFUs in a probiotic supplement while 16.9% of the respondents suggested the minimum should be one million CFUs. Less than one third of the respondents (29.5%) answered that they do not know what the minimum number of CFUs in a probiotic supplement should be. Regarding their knowledge of micro-organisms that may be contained in a probiotic supplement (Figure 1), the most recognized micro-organisms were *Lactobacillus acidophilus* (70.9%), *Lactobacillus reuteri* (69.2%), *Lactobacillus rhamnosus* (57.0%), *Bifidobacterium bifidum* (45.1%), *Saccharomyces boulardii* (28,3%), *Bacillus subtilis* (15.2%), *Enterococcus faecium* (7.2%), *Escherichia coli* (3.0%), *Streptococcus pyogenes* (2.5%), *Candida albicans* (2.1%), *Staphylococcus aureus* (1.7%), and *Mycobacterium avium* (1.3%).

Table 1: Relationship between demographics and knowledge, attitudes, and perceptions of pharmacists on the use of probiotics

Variables	Number of pharmacists (%)	Knowledge (%)				Attitudes			Perceptions		
		Good	Fair	Poor	X2 (p value)	Positive	Negative	X2 (p value)	Positive	Negative	X2 (p value)
Biological sex	237(100)				39.2132(0.047)			95.1638(0.024)			
Male	65(27.4)	12(18.5)	32(49.2)	21(32.3)		38(58.5)	27(41.5)		35(53.8)	30(46.2)	
Female	170(71.7)	14(8.2)	128(75.3)	28(16.5)		80(47.1)	90(52.9)		78(45.9)	92(54.1)	
Prefer not to say	2(0.8)	1(50.0)	1(50.0)	0(0.0)		1(50.0)	1(50.0)		0(0.0)	2(100.0)	
Age	237(100%)				92.4945(0.125)						110.9219 (0.712)
21-30 years old	97(40.9)	13(13.4)	66(68.0)	18(18.6)		51(52.6)	46(47.4)		53(54.6)	44(45.4)	
31-40 years old	81(34.2)	14(17.3)	60(74.1)	7(8.6)		37(45.7)	44(54.3)		37(45.7)	44(54.3)	
41-50 years old	17(7.2)	3(17.6)	13(76.5)	1(5,9)		10(58.8)	7(41.2)		8(47.1)	9(52.9)	
51-60 years old	24(10.1)	10(41.7)	14(58.3)	0(0.0)		13(54.2)	11(45.8)		6(25.0)	18(75.0)	
61-70 years old	12(5.1)	4(33.3)	8(66.7)	0(0.0)		7(58.3)	5(41.7)		8(66.7)	4(33.3)	
71-80 years old	5(2.1)	3(60.0)	1(20.0)	1(20.0)		1(20.0)	4(80.0)		1(20.0)	4(80.0)	
Prefer not to answer	1(0.4)	0(0.0)	1(100.0)	0(0.0)		0(0.0)	1(100.0)		0(0.0)	1(100.0)	
Highest degree obtained	237(100%)				51.4647(0.495)			191.4276(0.003)			64.6228(0.894)
Bachelor's degree	185(78.1)	20(10.8)	144(77.8)	21(11.4)		94(50.8)	91(49.2)		85(45.9)	100(54.1)	
Master's degree	37(13.6)	11(29.7)	23(62.2)	3(8.1)		17(45.9)	20(54.1)		18(48.6)	19(51.4)	
Doctorate	1(0.4)	0(0.0)	1(100.0)	0(0.0)		0(0.0)	1(100.0)		0(0.0)	1(100.0)	
Other	8(3.4)	3(37.5)	3(37.5)	2(25.0)		3(37.5)	5(62.5)		5(62.5)	3(37.5)	
Prefer not to say	6(2.5)	0(0.0)	5(83.3)	1(16.7)		2(33.3)	4(66.7)		5(83.3)	1(16.7)	
Year graduated Bachelor of Pharmacy	237(100%)				103.2375(0.179)						115.9658(0.932)
1961-1970	2(0.8)	0(0.0)	1(50.0)	1(50.0)		1(50.0)	1(50.0)		1(50.0)	1(50.0)	
1971-1980	9(3.8)	1(11.1)	8(88.9)	0(0.0)		5(55.6)	4(44.4)		4(44.4)	5(55.6)	
1981-1990	21(8.9)	12(57.1)	9(42.8)	0(0.0)		13(61.9)	9(38.1)		10(47.6)	11(52.4)	
1991-2000	23(9.7)	3(13.0)	19(82.6)	1(4.4)		12(52.2)	11(47.8)		8(34.8)	15(65.2)	
2001-2010	20(8.4)	3(15.0)	16(80.0)	1(5.0)		6(30.0)	14(70.0)		6(30.0)	14(70.0)	
2011-2020	137(57.8)	22(16.1)	93(67.9)	22(16.0)		64(46.7)	73(53.3)		70(51.1)	67(48.9)	
2021 or later	16(6.8)	3(18.8)	12(75.0)	1(6.2)		11(68.8)	5(31.2)		9(56.3)	7(43.7)	
Prefer not to answer	9(3.8)	1(11.1)	7(77.8)	1(11.1)		7(77.8)	2(22.2)		5(55.6)	4(44.4)	
University graduated	237(100%)				139.0936(0.277)			417.7753(0.007)			238.5135(0.032)
University 1	52(21.9)	9(17.3)	39(75.0)	4(7.7)		30(57.7)	22(42.3)		22(42.3)	30(57.7)	
University 2	26(11.0)	5(19.2)	19(73.1)	2(7.7)		10(38.5)	16(61.5)		9(34.6)	17(65.4)	
University 3	22(9.3)	3(13.6)	15(68.2)	4(18.2)		11(50.0)	11(50.0)		9(40.9)	13(59.1)	
University 4	16(6.8)	5(31.2)	9(56.3)	2(12.5)		9(56.3)	7(43.7)		5(31.3)	11(68.7)	
University 5	14(5.9)	3(21.4)	8(57.2)	3(21.4)		6(42.9)	8(57.1)		5(35.7)	9(64.3)	
University 6	49(20.7)	13(26.5)	33(67.4)	3(6.1)		26(53.1)	23(46.9)		30(61.2)	19(38.8)	
University 7	20(8.4)	1(5.0)	15(75.0)	4(20.0)		7(35.0)	13(65.0)		12(60.0)	8(40.0)	
University 8	5(2.1)	0(0.0)	4(80.0)	1(20.0)		2(40.0)	3(60.0)		2(40.0)	3(60.0)	
University 9	9(3.8)	1(11.1)	7(77.8)	1(11.1)		3(33.3)	6(66.7)		7(77.8)	2(22.2)	
Other	14(5.9)	3(21.4)	9(64.3)	2(14.3)		5(35.7)	9(64.3)		5(35.7)	9(64.3)	
Prefer not to say	10(4.2)	1(10.0)	8(80.0)	1(10.0)		8(80.0)	2(20.0)		7(70.0)	3(30.0)	

3.3 Attitudes towards probiotics

Attitude scores were categorized as positive if the total score was greater than or equal to the mean score and negative if it was below the mean score. Half of the respondents (51.3%) displayed positive attitudes toward probiotics as depicted in Table 2 (Mean ± SD = 43.33 ± 8.9). Regarding recommending probiotics to patients for various health conditions, the majority of respondents (92.4%) recommended probiotics for patients taking antibiotics (Table 4).

Table 2: Pharmacists' knowledge, attitudes, and perceptions score

Knowledge (%)				Attitudes (%)			Perceptions (%)		
Poor	**Fair**	**Good**	**Mean ± SD**	**Negative**	**Positive**	**Mean ± SD**	**Negative**	**Positive**	**Mean ± SD**
11.3	70.2	18.5	13.81 ±2.8	49.7	51.3	43.33±8.9	52.4	47.6	32.14±3.7

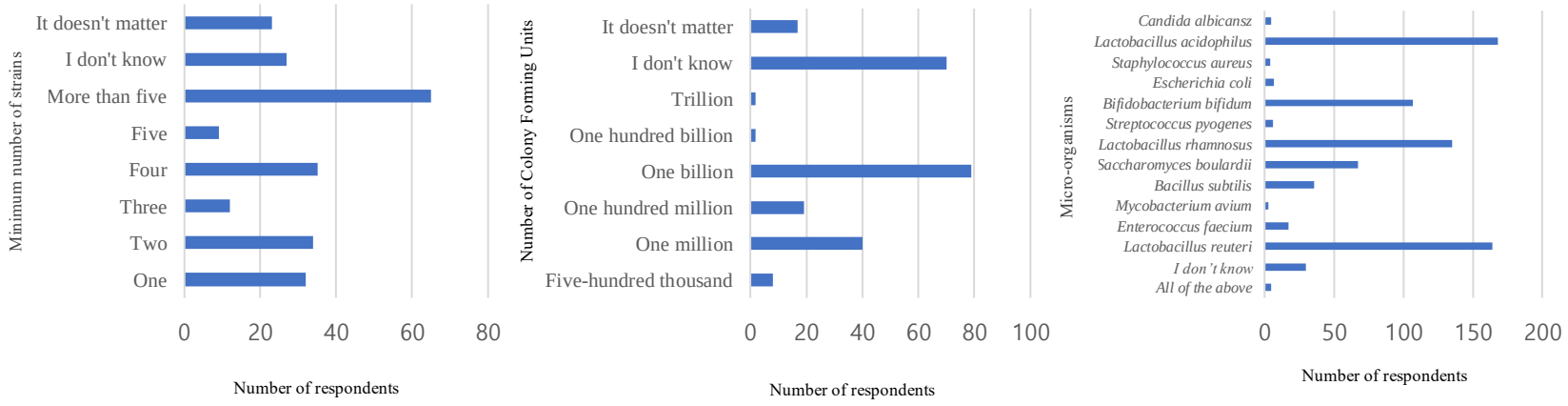


Figure 2: (a) The minimum number of strains that should be contained in a probiotic supplement selected by number of respondents. (b) The Colony Forming units that should be contained in a probiotic supplement selected by number of respondents. (c) Micro-organisms that may be contained in a probiotic supplement selected by number of respondents.

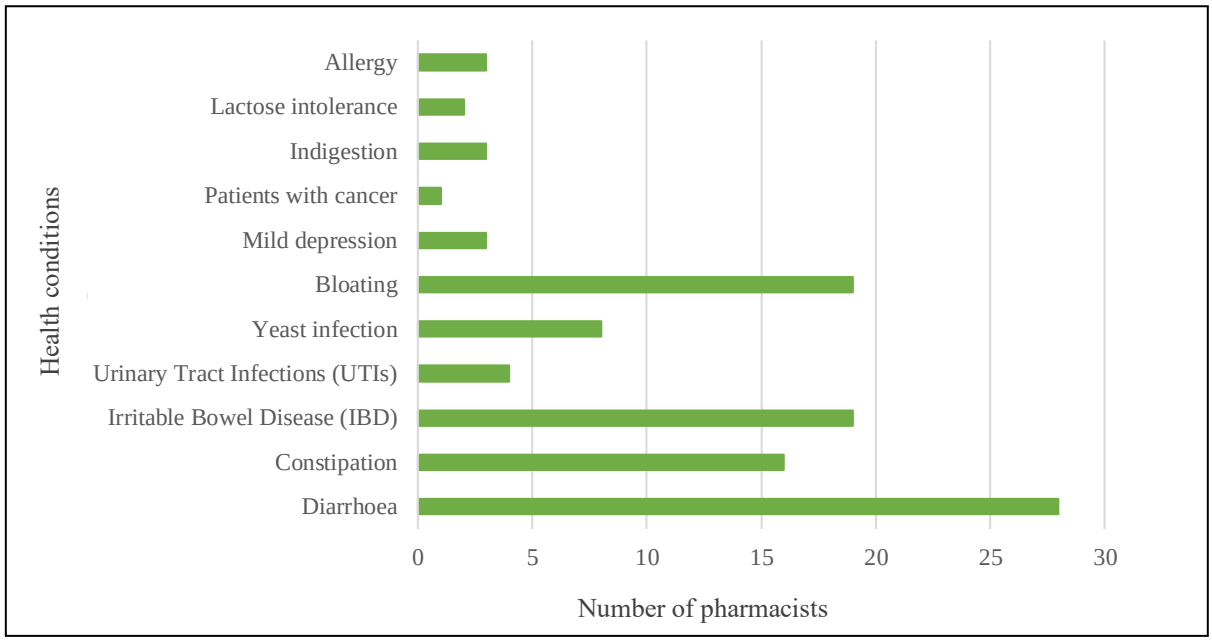


Figure 3: A summary of health conditions beyond those listed in the questionnaire for which respondents recommend the use of probiotics.

Table 3: Knowledge of respondents on the use of probiotics

Questions	**Correct answer n (%)**	**Incorrect answer n (%)**	**I don't know n (%)**
Probiotics contain live micro-organisms.	198(83.5)	27(11.4)	12(5.1)
Probiotics contain dead micro-organisms.	167(70.5)	42(17.7)	28(11.8)
Probiotics contain synthetic medicine.	179(75.5)	34(14.3)	28(11.8)
Probiotics contain herbs.	191(80.6)	24(10.1)	22(9.3)
Probiotics alter the intestinal microbiota.	198(83.5)	38(16.1)	1(0.4)
Probiotics confer an immunomodulatory effect.	157(66.2%)	51(21.5)	29(12.2)
Protics are effective as an adjuvant in *Helicobacter pylori* infection eradications.	168(70.9)	27(11.4)	42(17.7)
Probiotics assist with antibiotic side effects.	226(95.4)	9(3.8)	2(0.8)
Probiotics can carry antimicrobial resistant genes.	70(29.5)	120(50.6)	47(19.8)
There is a benefit to probiotics being antimicrobial resistant.	63(26.6)	92(38.8)	82(34.6)

Table 4: Attitudes and perceptions of respondents towards the use of probiotics

Questions	Positive n (%)	Negative n (%)	Neutral n (%)
Attitudes			
I recommend probiotics to patients taking antibiotics.	219(92.4)	12(5.1)	6(2.5)
I recommend probiotics to patients being treated for *H. pylori*.	124(52.4)	34(14.3)	79(33.3)
I recommend probiotics to patients for general health conditions.	167(70.5)	34(14.4)	36(15.2)
I provide advice on probiotics to patients.	210(84.8)	16(6.8)	20(8.4)
I recommend probiotics to patients for side effects of antibiotics.	208(87.8)	16(6.8)	13(5.5)
I have looked up to see how many strains of bacteria are contained in the probiotic dispensed.	149(62.9)	86(36.3)	2(0.8)
I have looked up to see the number of Colony Forming Units contained in the probiotic dispensed.	103(43.5)	130(54.9)	4(1.7)
I have looked up to see which micro-organisms may have antibiotic resistance.	50(21.1)	179(75.5)	8(3.4)
Perceptions			
Probiotics may be beneficial to patients.	92(92.4)	6(2.6)	12(5.1)
Probiotics may be harmful to patients.	29(12.2)	139(58.7)	69(29.1)
There is sufficient evidence regarding efficacy of probiotics.	137(57.8)	36(15.2)	64(27)
Health claims on probiotic labels can be trusted.	78(33.0)	67(28.3)	92(38.8)
There are appropriate guidelines on the use of probiotics in South Africa.	63(26.6)	95(40.1)	79(33.3)
It is the responsibility of a pharmacist to know about probiotics.	110(90.7)	5(2.1)	17(7.2)
I have an adequate knowledge on the use of probiotics.	55(43.4)	73(30.8)	61(25.7)
I would like to gain more information on probiotics.	220(92.8)	8(3.4)	9(3.8)

Additionally, more than half of the respondents (52.3%) recommended probiotics to patients being treated for *H. pylori*, while 70.5% recommended probiotics for general health conditions. Figure 2 lists health conditions for which respondents recommend probiotics beyond those specified in the survey. Notably, respondents highlighted the recommendation of probiotics for addressing diarrhoea (28 respondents), while some respondents advocated their use for both Irritable Bowel Disease and bloating (19 respondents). Additionally, respondents recommended probiotics for addressing constipation (16 respondents). This study displayed that 84.8% of the respondents provide advice on probiotics to patients. Majority of the respondents have shown interest in confirming specific aspects of the probiotics they dispensed, with 62.9% looking up to see how many strains of bacteria are contained in the probiotic dispense, 43.5% looking into the number of CFUs contained in the probiotic dispensed, and 75.5% looking up to see if micro-organisms may have antibiotic resistance (Table 4). The highest number of respondents (67.9%) indicated that they select a probiotic supplement based on what is on the prescription, followed by guidelines on the use of probiotics (36.7%), what is recommended by representatives (30.0%), colleagues (14.8%), articles (13.5%), internet (6.8%), and textbooks (6.8%). Other respondents explained that they use their personal experience, cost effectiveness, availability of stock, conferences, and lectures to select a probiotics supplement for patients.

3.4 Perceptions of probiotics

Perception scores were categorized as positive if the total score was greater than or equal to the mean score and negative if it was below the mean score. Less than half of the respondents (47.6%) of the respondents displayed positive perceptions of probiotics as depicted in Table 2 (Mean ± SD = 32.14 ± 3.7). The highest number of respondents (92.4%) answered that probiotics are beneficial to patients, and a small proportion of the respondents (12.2%) answered that probiotics may be harmful to patients (Table 4). More than half of the respondents (57.8%) agreed that there is sufficient evidence regarding efficacy of probiotics. However, there were less than half of the respondents (40.1%) who agreed that there are no appropriate guidelines on the use of probiotics in South Africa (Table 4). Less than half of the respondents (43.4%) agreed that they have adequate knowledge on the use of probiotics, and the majority of the respondents (90.7%) agree that it is the responsibility of a pharmacist to know about probiotics.

3.5 Relationship between demographics and knowledge, attitudes, and perceptions

Table 1 demonstrates the relationship between the demographics of the respondents and their knowledge, attitudes, and perceptions regarding the use of probiotics. There was a significant association of knowledge of probiotics with biological sexes ($X^2 = 39.2132$, $p < 0.05$). Female respondents had higher knowledge score (13.87 ± 2.6) than male respondents (13.68 ± 3.1).

There was a statistically significant difference in the demographics of respondents and their attitudes towards probiotics, including biological sex ($X^2 = 95.164$, $p < 0.05$), age ($X^2 = 248.008$, $p < 0.05$), highest degree obtained ($X^2 = 191.428$, $p < 0.05$), and the university from which they graduated ($X^2 = 417.775$, $p < 0.05$). Male respondents had a mean attitude score of 45.08 ± 8.4, while female respondents had a mean score of 42.68 ± 9.0. Respondents aged between 61 and 70 demonstrated the most positive attitudes towards probiotics, with a mean attitude score of 47.92 ± 7.9, with 58.3% expressing positive attitudes towards probiotics. University 1 had a mean attitude score of 44.50 ± 8.2, and 57.7% showing positive attitudes towards probiotics. University 6 had a mean attitude score of 44.47 ± 9.9 and University 4 had a mean attitude score of 43.75 ± 7.3.

There was a statistically significant difference in the demographics of respondents and their perceptions of probiotics, including age ($X^2 = 52.378$, $p < 0.05$), and the university of graduation ($X^2 = 238.514$, $p < 0.05$). Respondents aged between 61 and 70 showed the most positive perceptions towards probiotics, with a mean attitude score of 34.08 ± 3.2, and 66.7% expressing positive attitudes towards probiotics. Respondents from University 9 demonstrated had a mean attitude score of 33.78 ± 2.2, and 77.8% showing positive perceptions towards probiotics. University 6 had a mean attitude score of 33.04 ± 2.8 and University 3 had a mean attitude score of 32.50 ± 3.9.

3.6 Relationship between knowledge, attitudes, and perceptions

There was a statistically significant but weak correlation between the knowledge-attitudes variables ($r = 0.1537$, $p = 0.0179$) and attitude-perceptions variables ($r = 0.3214$, $p = 0.0000$). There was no statistically significant correlation between knowledge-perceptions variables ($r = 0.0092$, $p = 0.8879$). Table 5 displays the relationship between attitudes, perceptions, and knowledge of the respondents regarding the use of probiotics.

Table 5: Relationship between knowledge, attitudes, and perceptions

Variables	Correlation Coefficient	p-Value
Knowledge-Attitudes	0.1537	0.018
Knowledge-Perceptions	0.0092	0.888
Attitudes-Perceptions	0.3214	0.000

4. Discussion

The present study aimed to investigate the knowledge, attitudes, and perceptions of community pharmacists in South Africa regarding the use of probiotics. It investigated the relationship between demographic factors of the respondents and their knowledge, attitudes, and perceptions on this subject.

The findings from the respondents revealed that a significant portion of the respondents (70.2%) had a fair level of knowledge about probiotics, with only 13.5% demonstrating a good level of knowledge. A cross-sectional study in Pakistan revealed that 25.1% of pharmacists demonstrated a good level of knowledge about probiotics (Arshad *et al.*, 2021), while another study in India showed that 69.4% of the pharmacists had good knowledge (Soni *et al.*, 2018a). Additionally, other studies conducted in Iran and the United States of America (USA) report that pharmacists have higher levels of familiarity with probiotics among healthcare professionals (Payahoo *et al.*, 2012, Oliver *et al.*, 2014). The observed findings may be attributed to several factors, including the larger size of the probiotics market in the USA and Asia (Anukam *et al.*, 2006, Soni *et al.*, 2018a). In regions like the USA and Asia, there may be a higher level of familiarity with probiotics due to widespread marketing, higher availability of probiotic products, and a cultural emphasis on wellness and dietary supplements (Anukam *et al.*, 2006, Soni *et al.*, 2018a). It is important to note that the limited availability of information on probiotics in South Africa could contribute to the lower level of knowledge among respondents. Addressing these factors could be important in enhancing education and awareness of probiotics among pharmacists in South Africa. The differences in the level of knowledge about probiotics among pharmacists in this and previous studies may also be attributed to variations in the sample population, and the number and complexity of questions (Amarauche, 2015a, Chukwu *et al.*, 2015, Fijan *et al.*, 2019, Arshad *et al.*, 2021, Rahmah *et al.*, 2021).

Most respondents (95.4%) correctly recognized that probiotics help alleviate side effects of antibiotics. Additionally, 70.9% acknowledged that probiotics are effective as an adjuvant in managing *Helicobacter pylori* infections. The use of probiotics in preventing antibiotic-associated diarrhoea has been shown to reduce the risk associated with antibiotic-induced diarrhoea (Blaabjerg *et al.*, 2017).

Only 38.4% of the respondents answered correctly that it is necessary to consume probiotics for a long period to exert a beneficial effect. This finding contrasts with the results of an international survey on health professionals' knowledge of probiotics, which included pharmacists and other healthcare professionals, which reported that the majority of respondents (71.5%) agreed that probiotics should be consumed for a long period of time to exert a beneficial health effect (Fijan *et al.*, 2019). Determining the optimal duration for probiotic consumption to attain beneficial effects for specific health conditions can be challenging, mainly due to the limited evidence in studies regarding the recommended timeframe for taking probiotics (FAO and WHO, 2002, Shah *et al.*, 2021, Guarner *et al.*, 2023). There are studies that suggest an optimal duration for probiotic consumption to achieve beneficial effects. For example, a randomized clinical trial demonstrated that the daily intake of 10 billion CFUs of multi-strain probiotics, including *B. bifidum* W23, *B. lactis* W51, and *L. acidophilus* W37, significantly reduced overall risk of diarrhoea in children during the consumption of antibiotics and one week after the completion of the course (Lukasik *et al.*, 2022). A systematic review suggested that the treatment of acute gastroenteritis in children with *L. acidophilus* is effective when administered at a daily dosage of 10 billion CFUs daily, showing statistically significant improvement after three days of probiotic intake (Cheng *et al.*, 2022). While studies may provide some guidance on the use of probiotics, additional research is required to establish more precise recommendations on how to use probiotics.

Regarding the knowledge of micro-organisms that might be contained in a probiotic supplement, respondents most commonly recognized the *Lactobacillus* and *Bifidobacterium* strains. This may likely be because these strains are widely known and most commonly used as probiotics (Fijan, 2014, Hill *et al.*, 2014). Most respondents (70.9%) selected *L. acidophilus*, and this finding aligns with an international study where a significant proportion of respondents (92.0%) identified *L. acidophilus* as a potential micro-organism in a probiotic supplement

(Fijan *et al.*, 2019). The majority of the respondents (69.2%) selected *L. reuteri* in this study. Additionally, in this study, 71.5 % did not know that probiotics can carry antimicrobial resistant genes, and 73.4% of the respondents answered that there is a benefit to probiotics being resistant to antimicrobials. These respondents explained that one of the benefits of probiotic resistance to antibiotics is that probiotics remain unaffected by the antibiotic activity in the gut, ensuring the effectiveness of probiotics when taken concurrently with antibiotics. However, ingestion of antibiotic resistance genes could influence the pharmacodynamics of antibiotics (Gueimonde *et al.*, 2013). Antibiotic resistance, in most cases, is inherent to specific species or genera and is not typically transferable, posing minimal safety concerns (Salminen *et al.*, 1998). However, it is essential to carefully consider safety implications related to antibiotic resistance, especially in the context of plasmid-mediated resistance, which has the potential to transfer antibiotic resistance traits (Salminen *et al.*, 1998). *Lactobacillus reuteri* SD 2112 (ATCC 55730) has been identified as carrying transferrable antibiotic resistance to antibiotics, including clindamycin, cefotaxime, fusidic acid, penicillin, streptomycin, tetracycline, and vancomycin (Kastner *et al.*, 2006, Egervärn *et al.*, 2009, Szajewska *et al.*, 2014). It must be noted that *L. reuteri* was not included among the probiotic strains investigated in similar studies on the use of probiotics (Soni *et al.*, 2018b, Fijan *et al.*, 2019, Arshad *et al.*, 2021). This may be attributed to the fact that these studies did not study the aspect of antibiotic resistance in *L. reuteri* (Soni *et al.*, 2018b, Fijan *et al.*, 2019, Arshad *et al.*, 2021). Additionally, a small percentage of respondents (7.2%) selected *Enterococcus faecium.* Some respondents in a study conducted in Slovenia also recognized *Enterococcus faecium* as a micro-organism that might be contained in a probiotic supplement (Fijan *et al.*, 2019). *Enterococcus faecium* has been found to exhibit resistance to various antibiotics, including tetracyclines, ciprofloxacin, and vancomycin (Aleyasin *et al.*, 2007, Rathnayake *et al.*, 2012), which raises concerns about its suitability as a probiotic strain. Another group of respondents (3.0%) selected *Escherichia coli* as a potential probiotic strain, despite the fact that certain strains of *E. coli* are known to produce resistance to *β-lactam* antibiotics (Pitout, 2012, Anago *et al.*, 2015). These findings emphasize the importance of accurate knowledge regarding probiotic strains and their potential interactions with antibiotics. It is only after a probiotic strain has been identified, screened, and its mechanisms of action scientifically elucidated, that it can be accurately labelled (Donohue, 2006).

In terms of the respondents' knowledge of the minimum number of strains that should be contained in a probiotic supplement, only 5.1% of the respondents answered 'three strains.' Studies show that probiotics with multiple strains, including at least three different strains, may provide maximal efficacy (Giri *et al.*, 2014, Hao *et al.*, 2014, Kuebutornye *et al.*, 2020). Additionally, a significant portion of respondents (33.3%) believed that there should be a minimum number of 10^9 CFUs in a probiotic supplement. Studies recommend a daily intake of at least 10^9 CFUs for optimal efficacy (Johnston *et al.*, 2006, Minelli and Benini, 2008, Kechagia *et al.*, 2013). These findings highlight a potential gap in knowledge among the respondents regarding the minimum requirements of probiotic supplements. Specifically, 36.3% of the respondents reported not checking the number of bacterial strains in the probiotic dispensed, and 54.9% did not verify the CFUs in the probiotic dispensed. This emphasizes the importance of targeted education and awareness programs to address these knowledge gaps. Studies on the use of probiotics also stated that the implementation of educational interventions, potentially delivered over an extended period, could improve knowledge and awareness of healthcare professionals on probiotics (Amarauche, 2015a, Soni *et al.*, 2018b, Fijan *et al.*, 2019). Respondents (90.7%) agreed that it is the responsibility of a pharmacist to know about probiotics, indicating a strong interest among respondents in gaining more information about probiotics, with 92.8% expressing their desire for additional knowledge. Furthermore, 84.4% of the participants expressed a willingness to engage in training programs or educational initiatives focused on the use of probiotics. While the intended sample size could have led to more accurate results, the respondents' willingness to learn and participate in training suggests a potential for targeted educational interventions to enhance understanding and awareness among pharmacists.

Concerning respondents' perceptions on the safety of probiotics, 15.2% of the respondents disagreed that there is sufficient evidence regarding the efficacy of probiotics, and 28.3% expressed that health claims on probiotic labels cannot be trusted. These results also align with the analysis of probiotic and prebiotic-containing foods and supplements manufactured in South Africa (Brink *et al.*, 2005). It has revealed that these products often mislead consumers with scientifically inaccurate health claims (Brink *et al.*, 2005). Additionally, the study found that the information regarding the number of bacterial strains on product labels was frequently incorrect (Brink *et al.*, 2005). Therefore, it is crucial for pharmacists to have direct access to scientific information provided by probiotic companies. Pharmacists can use company

websites where scientific data and educational publications are readily available. Moreover, as a means of ensuring product quality and transparency, product labels should prominently feature the complete name of the probiotic strain and ensure the minimum live count of these strains throughout the product's shelf-life.

A significant but weak correlation between knowledge and attitude was identified ($r = 0.1537$, $p = 0.0179$). This indicates that respondents who had higher level of knowledge also had a more positive attitude towards probiotics, although the correlation was weak. This finding aligns with previous studies that also showed weak correlations between knowledge and attitude on probiotics (Soni *et al.*, 2018b, Rahmah *et al.*, 2021). However, it must be noted that these studies encompassed a broader spectrum of healthcare professionals and students.

The correlation between attitudes and perception was also significant but weak ($r = 0.3214$, $p = 0.000$). This suggests that respondents with a more positive attitude also had a more positive perception towards probiotics, although the correlation was weak. There is no statistically significant correlation between knowledge-perceptions variables ($r = 0.0092$, $p = 0.8879$). This suggests that respondents with a higher level of knowledge did not necessarily have positive perceptions. These findings emphasize the complexity of factors influencing individuals' knowledge, attitudes and perceptions regarding probiotics.

5. Conclusion

The current study has identified predominantly limited knowledge regarding the use of probiotics among respondents, despite their positive attitudes and perceptions towards the use of probiotics. To bridge the gap between knowledge and positive attitudes and perceptions, targeted training programs focused on probiotic use should be initiated, given that the market for probiotic consumption is growing rapidly. The study has emphasized the complexity of factors influencing individuals' knowledge, attitudes, and perceptions regarding probiotics. Pharmacists' interest in probiotics should be acknowledged and targeted learning programs for the future and current pharmacists is imperative to prevent inappropriate use of these agents.

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Author contributions:

The initial concept and draft of the article were developed by Ané Orchard, Razeeya Khan, and Muhammed Vally. Yedam Kim undertook the data collection. Data analysis was undertaken by Yedam Kim and Ané Orchard. Yedam Kim drafted the original article, and Ané Orchard, Razeeya Khan, and Muhammed Vally reviewed the article.

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Data availability

The sharing of data is not applicable to this article since no new data was generated or analysed in the course of this study.

Disclaimer:

The authors declare that the perspectives presented in the submitted article are their own and do not represent the official stance of the institution or funding entity.

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CHAPTER 4 - OVERVIEW

4. 1 Study highlights

Objectives one to three were successfully completed within the chapter 3.

After investigating the use of probiotics in community pharmacies in South Africa and assessing pharmacists' knowledge, attitudes and perceptions, the findings revealed that 18.5% demonstrated a good level of knowledge about probiotics, while 11.3% showed a poor level of knowledge (Mean ± SD = 13.81 ± 2.8). Regarding attitudes, half of the respondents (51.3%) displayed positivity toward probiotics, while 49.7% exhibited negative attitudes (43.33 ± 8.9). Less than half of the respondents (47.6%) had positive perceptions of probiotics.

The findings revealed that there was a significant association of knowledge of probiotics with biological sexes (X^2 =39.2132, $p < 0.05$). There was also a statistically significant difference in the biological sex of respondents and their attitudes towards probiotics (X^2 =95.164, $p < 0.05$). Additionally, there was a statistically significant difference in the age of respondents and their attitudes towards probiotics (X^2 = 248.008, $p < 0.05$). The highest degree obtained, as well as the university attended by respondents, displayed statistically significant differences in their attitudes towards probiotics (X^2 = 191.428, $p < 0.05$; X^2 = 417.775, $p < 0.05$, respectively).

The findings revealed that there was a statistically significant and weak correlation between the knowledge-attitudes variables (r = 0.1537, p = 0.0179) and attitude-perceptions variables (r = 0.3214, p = 0.0000). There was no statistically significant correlation between knowledge-perceptions variables (r = 0.0092, p = 0.8879).

4.2 Limitations

An important limitation of the study was the discrepancy between the number of individuals who initiated the survey and the actual number of completed questionnaires (n = 273). This may have attributed from various factors. Some pharmacists may have felt that they lacked sufficient knowledge to provide accurate responses to the survey questions, while others might

have disagreed with the nature of the questions (Fijan *et al.*, 2019). Consequently, it is plausible that respondents who possessed a certain level of knowledge about probiotics were more likely to participate, as opposed to those who had limited knowledge or none at all (Fijan *et al.*, 2019). Additionally, the disparities noted in knowledge, attitudes, and perceptions across various demographics might be explained by variations in the number of respondents associated with demographic factors, including biological sexes. It must also be noted that there have been limited studies exclusively focused on determining the knowledge, attitudes, and perceptions of pharmacists, which could contribute to the variations in findings between different studies (Amarauche, 2015a, Chukwu *et al.*, 2015, Fijan *et al.*, 2019, Arshad *et al.*, 2021, Rahmah *et al.*, 2021).

4.3 Significance of the study

This study aimed to address a significant gap in understanding the knowledge, attitudes and perceptions of probiotics among pharmacists. Despite the increasing recognition of the importance of probiotics in promoting gut health, they are currently classified as complementary and alternative medicine and are not typically integrated into pharmacy education programs. Given that probiotics are readily available in pharmacies, pharmacists are expected to have appropriate knowledge and attitudes to offer advice and recommend suitable probiotics. Thus, this study identified whether pharmacists are equipped with the knowledge and attitudes needed to provide the counselling and recommendations, or whether education interventions are needed. This study has also reviewed the literature relating to probiotic recommendation and counselling.

4.4 Future considerations

Recommendation for research

The limited research on probiotic use in South Africa highlights the necessity for investigating different aspects related to pharmacists' comprehension of probiotics. This includes understanding decision-making processes behind recommending or selecting a probiotic supplement by pharmacists, their level of education in probiotics, and their comprehension of the associated risks and benefits. While studies may provide some guidance on the use of probiotics, additional research is required to establish more precise evidence-based

recommendations. This includes addressing the criteria and methodologies for probiotic selection and evaluation how to use probiotics.

Recommendation for practice

It is recommended that pharmacists use probiotics meeting the minimum requirements. It is essential that benefits of using probiotics significantly outweigh the associated risks for pharmacists to recommend a probiotic for specific health conditions. Safety considerations associated with probiotics must be taken into account when providing probiotics to patients. Pharmacists should also inform patients about potential side effects of probiotics and offer appropriate counselling to ensure their well-being and safety. Initiatives aimed at enhancing pharmacists' understanding of probiotics, along with the development of dispensing protocols, could contribute to improved practices in the pharmacy setting in South Africa.

4.5 Conclusion

This is the first study to investigate knowledge, attitudes, and perceptions of community pharmacists in South Africa on the use of probiotics. The current study has identified limited knowledge regarding the use of probiotics among respondents, despite their positive attitudes and perceptions towards the use of probiotics. Pharmacists' interest in probiotics should be acknowledged and targeted learning programs for the future and current pharmacists is imperative to ensure rational use of probiotics.

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APPENDICES

Appendix A: Survey

Demographics **PLEASE SELECT THE ANSWER THAT MOST REPRESENTS YOUR VIEW**	
Are you a pharmacist?	◯ Yes ◯ No
Are you currently working in a community pharmacy in South Africa?	◯ Yes ◯ No
Geographic region of pharmacy	◯ 1. Eastern Cape ◯ 2. Free State ◯ 3. Gauteng ◯ 4. KwaZulu-Natal ◯ 5. Limpopo ◯ 6. Mpumalanga ◯ 7. Northern Cape ◯ 8. North West ◯ 9. Western Cape ◯ 10. Out of South Africa ◯ 11. Prefer not to answer
Biological sex	◯ 1. Male ◯ 2. Female ◯ 3. Other ◯ 4. Prefer not to answer
Age	◯ 1. 21-30 years old ◯ 2. 31-40 years old ◯ 3. 41-50 years old ◯ 4. 51-60 years old ◯ 5. 61-70 years old ◯ 6. 71-80 years old ◯ 7. Prefer not to answer
Highest degree obtained	◯ 1. Bachelor's degree ◯ 2. Master's degree ◯ 3. Doctorate ◯ 4. Other _____ ◯ 5. Prefer not to answer
Year graduated Bachelor of pharmacy from university.	◯ 1. Before 1960 ◯ 2. 1961-1970 ◯ 3. 1971-1980 ◯ 4. 1981-1990 ◯ 5. 1991-2000 ◯ 6. 2001-2010 ◯ 7. 2011-2020 ◯ 8. 2021 or later ◯ 9. Prefer not to answer

University graduated

- ○ 1. North-West University
- ○ 2. Rhodes University
- ○ 3. University of Kwazulu-Natal (Durban-Westville)
- ○ 4. Nelson Mandela University (University of Port Elizabeth)
- ○ 5. University of Western Cape
- ○ 6. University of Witwatersrand
- ○ 7. Sefako Makgatho Health Sciences University (Previously MEDUNSA)
- ○ 8. Stellenbosch University
- ○ 9. University of Limpopo
- ○ 10. Other _____
- ○ 11. Prefer not to answer

Knowledge

PLEASE SELECT THE ANSWER THAT MOST REPRESENTS YOUR VIEW

	Yes	No	I don't know
All bacteria cause infections.	○	○	○
Probiotics contain live microorganisms.	○	○	○
Probiotics contain dead microorganisms.	○	○	○
Probiotics contain synthetic medicine.	○	○	○
Probiotics contain herbs.	○	○	○
Probiotics alter the intestinal microbiota.	○	○	○
Probiotics confer an immunomodulatory effect.	○	○	○
It is necessary to consume probiotics for a long time to exert a beneficial effect.	○	○	○
Probiotics are effective as an adjuvant in Helicobacter pylori infection eradications.	○	○	○
Probiotics can carry antimicrobial resistant genes.	○	○	○
Probiotics are only effective in the form of tablets.	○	○	○
Symptoms such as bloating, constipation and diarrhoea are the side effects of probiotics.	○	○	○
Any probiotic supplement on the market can be considered effective.	○	○	○
Probiotics assist with antibiotic side effects.	○	○	○
If a person takes probiotics with antibiotics, the combined oral contraceptive is not rendered ineffective.	○	○	○
There is a benefit to probiotics being antimicrobial resistant.	○	○	○

Based on your current knowledge, what is the minimum number of strains that should be contained in a probiotic supplement?	◯ 1. one ◯ 2. two ◯ 3. three ◯ 4. four ◯ 5. five ◯ 6. more than five ◯ 7. I don't know ◯ 8. It doesn't matter
On a probiotic supplement, it states how many colony forming units of the microorganisms are available. What is the minimum number of colony forming units that should be contained in a probiotic supplement based on your current knowledge?	◯ 1. Five-hundred thousand ◯ 2. One million ◯ 3. One hundred million ◯ 4. One billion ◯ 5. One Hundred billion ◯ 6. One trillion ◯ 7. I don't know ◯ 8. It doesn't matter
Select the microorganisms that may be contained in a probiotic supplement.	☐ 1. Candida albicans ☐ 2. Lactobacillus acidophilus ☐ 3. Staphylococcus aureus ☐ 4. Escherichia coli ☐ 5. Bifidobacterium bifidum ☐ 6. Streptococcus pyogenes ☐ 7. Lactobacillus rhamnosus ☐ 8. Saccharomyces boulardii ☐ 9. Bacillus subtilis ☐ 10. Mycobacterium avium ☐ 11. Enterococcus faecium ☐ 12. Lactobacillus reuteri ☐ 13. I don't know ☐ 14. All of the above ☐ 15. None of the above

Attitudes

PLEASE SELECT THE ANSWER THAT MOST REPRESENTS YOUR VIEW

*** Take note of which side of the options represents your view correctly**

	Strongly disagree	Disagree	Neutral (I don't know)	Agree	Strongly agree
I recommend probiotics to patients taking antibiotics.	○	○	○	○	○
I recommend probiotics to patients being treated for H. pylori.	○	○	○	○	○
I recommend probiotics to patients for general health conditions.	○	○	○	○	○
I provide advice on probiotics to patients.	○	○	○	○	○
I recommend probiotics to patients for side effects of antibiotics.	○	○	○	○	○

If agree, or strongly agree to recommend probiotics to patients being treated for H. pylori, what did you recommend to your patient? For example, what regimen, how often etc. _____

If agree, or strongly agree to recommend probiotics to patients for general health conditions., which health conditions? _____

Attitudes

	Yes	No	I don't know
I have looked up to see how many strains of bacteria are contained in the probiotic dispensed.	○	○	○
I have looked up to see the number of Colony Forming Units (CFUs) contained in the probiotic dispensed.	○	○	○
I have looked up to see if the micro-organisms in the probiotic being dispensed are live bacteria.	○	○	○
I have looked up to see which micro-organisms may have antibiotic resistance	○	○	○
I have had a discussion on the use of probiotics with colleagues in the pharmacy.	○	○	○
I can name more than 4 probiotic products available in the pharmacy.	○	○	○
I have recommended a specific probiotic to the patient.	○	○	○

If yes, which probiotic did you recommend? For example, brand, product name,etc. _____

How do you select a probiotic supplement for your patient?

- ☐ 1. Based on what is on the prescription
- ☐ 2. Guidelines on the use of probiotics
- ☐ 3. Internet
- ☐ 4. Articles
- ☐ 5. Colleagues
- ☐ 6. Textbooks
- ☐ 7. Based on what is recommended by reps
- ☐ 8. I have never selected a probiotic for a patient
- ☐ 9. Other _____

Perceptions

PLEASE SELECT THE ANSWER THAT MOST REPRESENTS YOUR VIEW

*** Take note of which side of the options represents your view correctly**

	Strongly disagree	Disagree	Neutral (I don't know)	Agree	Strongly agree
Probiotics are beneficial to patients.	○	○	○	○	○
Probiotics may be harmful to patients.	○	○	○	○	○
There is sufficient evidence regarding efficacy of probiotics.	○	○	○	○	○
Health claims on probiotic labels can be trusted.	○	○	○	○	○
There are appropriate guidelines on the use of probiotics in South Africa.	○	○	○	○	○
It is the responsibility of a pharmacist to know about probiotics.	○	○	○	○	○
I have adequate knowledge on the use of probiotics.	○	○	○	○	○
I would like to gain more information on probiotics.	○	○	○	○	○
I am willing to participate in trainings or programmes on the use of probiotics.	○	○	○	○	○

If agree, or strongly agree, what circumstances do you think probiotics are harmful to patients?

_____

Appendix B: Participant Information Sheet

:

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Participant Information Sheet

Use of probiotics in community pharmacy in South Africa: a survey of pharmacist attitudes, perceptions, and knowledge.

Dear Sir / Madam

My name is Yedam Kim. I am a Masters student in Clinical Pharmacy at the University of the Witwatersrand, Johannesburg. My supervisors are Dr Ané Orchard, Razeeya Khan, and Muhammed Vally. I am conducting a research study about the use of probiotics in community pharmacies in South Africa. The study title is: Use of probiotics in community pharmacy in South Africa: a survey of pharmacist attitudes, perceptions, and knowledge.

I am inviting you to take part to answer a questionnaire.

The survey will be confidential and anonymous. When I share the results of the research study, I will not include your name or anything else that could identify you. With your permission, other researchers may use the data collected from this research study, but your name and any personal information will not be used or passed on. Only the researcher and the supervisors will have access to the data.

If you decide to take part in the research study, it should be because you want to volunteer. You do not have to take part. You can stop participating in the study at any time. You do not have to answer any questions if you do not want to. You will not get any direct benefits if you choose to join the research study. You will not lose any services, benefits or rights you would normally have

if you decided not to join. Taking part in the research study will not cost you anything. You will not be paid for being in this research study.

The risks for this research study are no more than what happens in everyday life.

This research study will be written up as a research report and/or article. The report will be available on the university library website and articles. If you would like to receive a summary of this report, I will be happy to send it to you.

If you have any questions during or afterwards about this research study, feel free to contact me on the details listed below. If you have any concerns or complaints about the ethical procedures of this research study, you are welcome to contact the University Human Research Ethics Committee (Non-Medical), telephone +27(0) 11 717 1408, email hrecnon-medical@wits.ac.za.

Appendix C: Participant Consent

Participant Consent

Use of probiotics in community pharmacy in South Africa: a survey of pharmacist attitudes, perceptions, and knowledge.

I hereby confirm that I have accurately read and understood the information sheet provided by the researcher, and I understand the following:

• I understand that participation is voluntary, and that I will not be penalised for non-participation

Yes	No

• I understand that I may withdraw from the study at any time and that withdrawal at any stage does not incur any harm or penalty

Yes	No

• I understand that the researcher will use my responses for furthering research, education and training

Yes	No

• I understand that I have the right to not answer any questions I do not feel comfortable answering

Yes	No

• I understand that my privacy will be respected, and that my personal identifiable details will not be made available I hereby agree that I have understood the requirements of this project and I am willing to participate in the survey.

Yes	No

_____ _____

Signed by participant Date

Appendix D: Ethics Clearance (Medical) Letter

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research and Innovation)

TO: Ms Y Kim
School of Therapeutic Sciences
Department of Pharmacy and Pharmacology
Medical School
University

E-mail: 1825217@students.wits.ac.za

CC: Supervisor: Mr M Valley; Ms R Khan; Dr A Orchard
<Muhammed.Valley@wits.ac.za>
and <HREC-Medical Research Office@wits.ac.za>

FROM: Mr Iain Burns
Human Research Ethics Committee (Medical)
Tel: 011 717 1252

E-mail: Iain.Burns@wits.ac.za

DATE: 2022/11/07

REF: R14/49

PROTOCOL NO: **M220810** (This is your ethics application reference number. Please quote it in all enquiries, oral or written, relating to this study.)

PROJECT TITLE: *Use of probiotics in community pharmacies in South Africa: a survey of pharmacist attitudes, perceptions and knowledge*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to Government funding of the University.



MSWorks2000/Iain0007/Clearscan.wps

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R49 Ms Y Kim

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M220810

NAME: (Principal Investigator)	Ms Y Kim
DEPARTMENT:	School of Therapeutic Sciences Department of Pharmacy and Pharmacology Medical School University
PROJECT TITLE:	*Use of probiotics in community pharmacies in South Africa: a survey of pharmacist attitudes, perceptions and knowledge*
DATE CONSIDERED:	2022/08/26
DECISION:	Approved unconditionally
CONDITIONS:	
NOTE:	If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>
SUPERVISOR:	Mr M Valley; Ms R Khan; Dr A Orchard
APPROVED BY:	Dr N Naran, Co-Chairperson, HREC (Medical)
DATE OF APPROVAL:	2022/11/07

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **August** and therefore reports and re-certification will be due in the month of **August** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator _____ Date _____

Appendix E: Approval of Protocol Letter

UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG

Private Bag 3 Wits, 2050
Fax: 027117172119
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Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

05 October 2022
Person No: 1825217
PAG

Ms Y Kim
Wits Junction
Junction Avenue
Parktown
2193
South Africa

Dear Ms Yedam Kim

Master of Pharmacy: Approval of Title

We have pleasure in advising that your proposal entitled *Use of probiotics in community pharmacy in South Africa: A survey of pharmacist attitudes, perceptions, and knowledge* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

Appendix F: Ethics Waiver (Medical) for Literature Review

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research & Innovation)

14/06/2023

Ref: W-CBP-230614-01

TO WHOM IT MAY CONCERN:

Waiver:	This certifies that the following research does not require clearance from the Human Research Ethics Committee (Medical)	
Principal Investigator:	Miss Yedam Kim et al	Student No.: 1825217
Supervisor:	Dr Ané Orchard	
School:	School of Therapeutic Sciences	
Department:	Pharmacy and Pharmacology	
Project title:	*Use of probiotics in community pharmacy in South Africa: a survey of pharmacist attitudes, perceptions, and knowledge.*	
Reason:	A review of information in the public domain. No human participants will be involved in the study.	

Dr CB Penny

Chairperson: Human Research Ethics Committee (Medical)

Research Office Secretariat: Faculty of Health Sciences, Phillip Tobias Health Sciences Building, 3rd Floor, Office 301/2/4, 29 Princess of Wales Terrace, Parktown, 2193

Private Bag 3, Wits 2050

Office email: HREC-Medical.ResearchOffice@wits.ac.za
Website: https://www.wits.ac.za/research/researcher-support/research-ethics/ethics-committees/

Appendix G: Letter of Data Request Acceptance from SAPC

South African Pharmacy Council

Registered Office
SAPC Building
591 Belvedere Street
Arcadia, Pretoria,0083

Postal Address
Private Bag X40040
Arcadia, 0007

Customer Care Line
0861 7272 00

Fax
(27)12-321 1492 /1479

E-mail
customercare@sapc.za.org

Website
www.sapc.za.org

COMPANY SECRETARY & LEGAL SERVICES

MS Y KIM

Email: 1825217@students.wits.ac.za

Your Reference	Our Reference	Date
P58317	SAPCCL/DG HOFFMANN	8 August 2023

Dear Ms Kim

MASTERS IN PHARMACY:
USE OF PROBIOTICS IN COMMUNITY PHARMACIES IN SOUTH AFRICA: A SURVEY OF PHARMACIST ATTITUDES, PERCEPTIONS AND KNOWLEDGE

We refer to the abovementioned matter and in particular the request for contact details of pharmacists in South Africa in order to conduct research by Ms Kim for purposes of a Masters in Pharmacy, where the project is identified as:

"use of probiotics in community pharmacies in South Africa: a survey of pharmacist attitudes, perceptions and knowledge"

We confirm that the request for the information was accompanied by the appropriate ethics approval from the University of the Witwatersrand Human Research Ethics Committee (Medical) under Clearance Certificate Number M220810.

Attached hereto please find the requested data, which is includes the details of pharmacists in South Africa, which data includes only email addresses, as the South African Pharmacy Council will not permit the distribution of personal information such as cellular phone numbers.

Kindly note that:

(a) The registers kept by the Registrar in terms of section 14 of the Pharmacy Act, 53 of 1974 may change consistently. For this reason, the Registrar can only guarantee the accuracy of the information as at the time the register was drawn off our data system; and

(b) The accuracy of the information provided is not guaranteed by the Registrar as it relies on the accuracy of information provide by registered persons.

Kindly note further the following strict conditions in processing and using the data provided shall be adhered to at all times:

(a) The data may be used exclusively for the research project as identified in the Human Research Ethics Committee (Medical) approval;

(b) The data may only be used by the researcher and may not be given or sold to any other person for use or distribution thereof, and must be protected from such distribution at all times;

(c) Emails to the pharmacists must explain that the information is for approved research purposes only;

(d) Communication to the pharmacists must allow for an opt out of receiving email communication/further communication; and

(e) The outcome of the research must be shared with the South African Pharmacy Council.

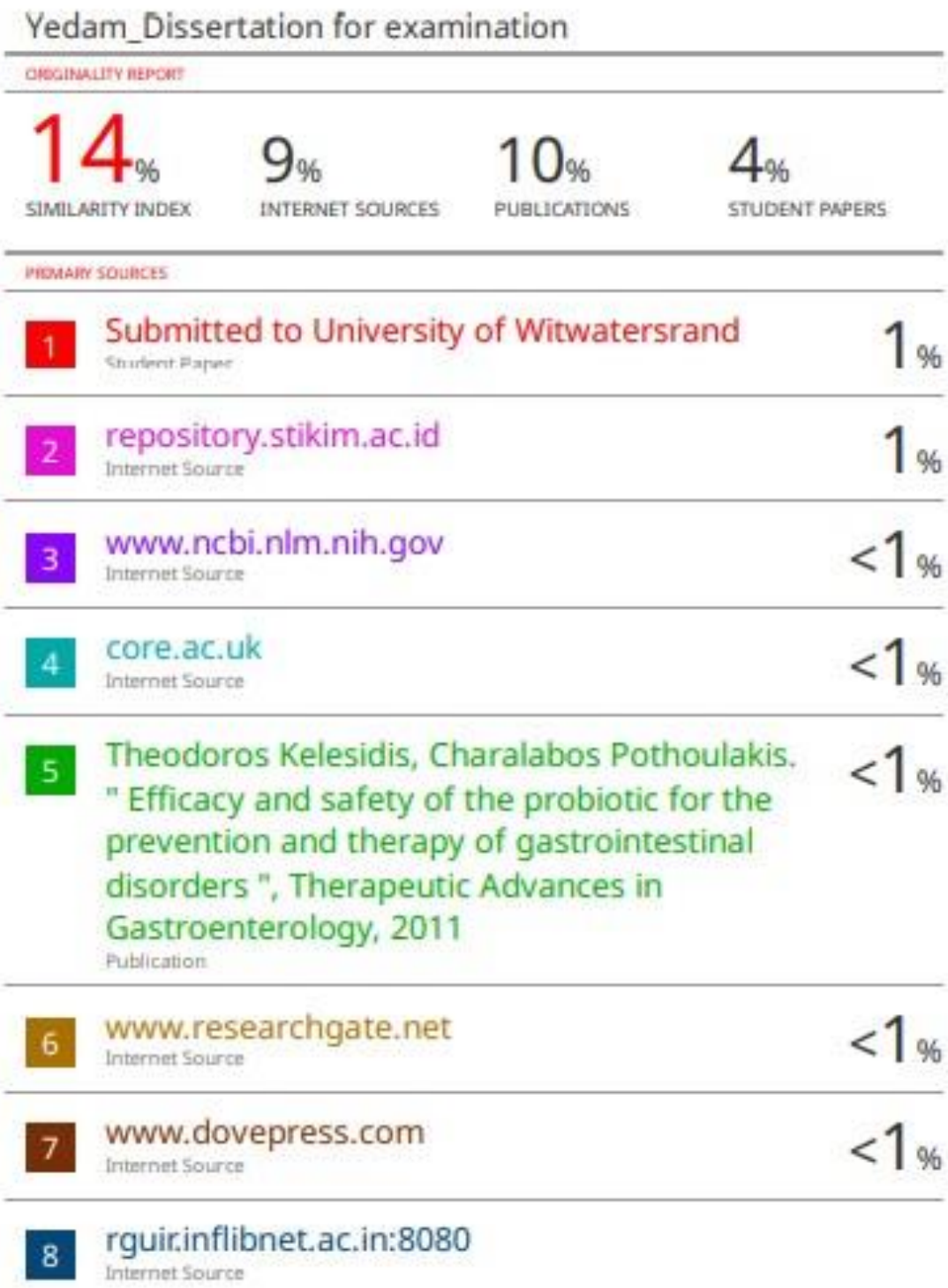
Failure to adhere to the conditions herein, will result in disciplinary action been taken against you in terms of Section 39 of the Pharmacy Act, 53 of 1974.

Yours faithfully



for REGISTRAR

Appendix H: Turnitin Report



Yedam_Dissertation for examination

ORIGINALITY REPORT

14%	9%	10%	4%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Submitted to University of Witwatersrand Student Paper	1%
2	repository.stikim.ac.id Internet Source	1%
3	www.ncbi.nlm.nih.gov Internet Source	<1%
4	core.ac.uk Internet Source	<1%
5	Theodoros Kelesidis, Charalabos Pothoulakis. " Efficacy and safety of the probiotic for the prevention and therapy of gastrointestinal disorders ", Therapeutic Advances in Gastroenterology, 2011 Publication	<1%
6	www.researchgate.net Internet Source	<1%
7	www.dovepress.com Internet Source	<1%
8	rguir.inflibnet.ac.in:8080 Internet Source	