ANTIBIOFILM EFFECTS OF *Limosilactobacillus reuteri* 29A CELL-FREE SUPERNATANT AGAINST MAJOR *Candida* SPECIES IN MURINE MODEL OF VULVOVAGINAL CANDIDIASIS

By

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Postbiotics are metabolites secreted from live microorganisms in their cell-free supernatants and are strain dependent. They can mimic the beneficial therapeutic effects of probiotics while avoiding the risk of administering live microorganisms, coupled with having longer shelf-life. Lactic acid bacteria (LAB) such as *Lactobacillus* species which are commonly employed as probiotics, are native members of a healthy vaginal microbiota, and their dominance is crucial for an eubiotic vaginal ecosystem. They confer protection through various mechanisms including production of postbiotics. One of the major disorders affecting vaginal health is vulvovaginal candidiasis (VVC) and its reoccurrence, caused by *Candida* species including *Candida albicans* and *Candida glabrata*. The aforementioned *Candida* species, notably *C. albicans* is a biofilm producing pathogen and habitually forms part of the vaginal microbiota. Latest research has implicated the role of fungal biofilms in VVC, particularly in the setting of treatment failure and recurrence. Hence, in this study, we aimed to evaluate the antibiofilm activity of postbiotics produced by *Limosilactobacillus reuteri* 29A, *in vitro* and in VVC murine model. The cell-free supernatant (CFS) was derived from fresh 48 h anaerobically cultured *L. reuteri* 29A strain in De Man, Rogosa and Sharpe (MRS) broth. It was filter sterilized before introducing to preformed biofilms of *C. albicans* (ATCC 14053), *C. glabrata* (ATCC 2001) reference isolates and *C. albicans* (S.21), *C. glabrata* (95670) clinical isolates. Specifically, *L. reuteri* 29A CFS destroyed 91% of *C. albicans* ATCC 14053 and 92% of *C. albicans* S.21 biofilms. For *C. glabrata* isolates, *L. reuteri* 29A CFS inhibited 86% of ATCC 2001 and 83% for *C. glabrata* 95670 biofilms. The mechanism of the CFS was dependent on its low pH level. Metabolites produced in *L. reuteri* 29A CFS were identified by Gas Chromatography-Mass Spectrophotometry. Scanning electron microscopy (SEM) displayed the destruction of preformed biofilms and impediment of *C. albicans* morphogenesis after postbiotics administration *in vitro*. The present study also aimed to investigate the role of the CFS in VVC murine model. BALB/c female mice were inoculated intravaginally

with cell suspensions of the clinical isolates of *Candida* species before treatment with *L. reuteri* 29A CFS. Microbiological and cytological examinations revealed that *C. albicans* yeast to hyphae formation was inhibited and prohibited after *L. reuteri* 29A CFS administration, via eliciting the hosts immune response. Histopathological examination revealed the formation of *Candida* species biofilms on the vagina epithelium. However, after treatment with *L. reuteri* 29A CFS, desecrated vaginal tissues were restored through *Candida* species biofilm inhibition. SEM *in vivo* further displayed the reinstatement of a bacterial microflora. Colony forming unit count showed the reduction of fungal burden in infected mice after *L. reuteri* 29A CFS administration. Although the efficacy of the postbiotics *L. reuteri* 29A has been proven in *in vitro* and murine model, its limitation includes its application among human subjects. Overall, the results of this study demonstrate the potential use of the postbiotics of *L. reuteri* 29A as an adjuvant to treat and/or prevent *Candida* related vaginal infections.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk Ijazah Master Sains

KESAN ANTIBIOFILEM *Limosilactobacillus reuteri* 29A SUPERNATAN BEBAS SEL TERHADAP SPESIES *Candida* UTAMA DALAM MODEL MURINE KANDIDIASIS VULVOVAGINAL

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Posbiotik ialah metabolit yang dirembeskan oleh mikroorganisma hidup dan didapati dalam supernatan bebas sel dan ia bergantung kepada jenis stren bakteria. Posbiotik boleh memberi kesan terapeutik berfaedah seperti probiotik. Ia mengelakkan risiko pemberian mikroorganisma hidup secara terus dan mempunyai umur simpan yang lebih lama. Bakteria asid laktik (LAB) seperti spesis *Lactobacillus* biasa digunakan sebagai probiotik, adalah ahli asli mikrobiota faraj yang sihat, dan penguasaannya adalah penting untuk ekosistem faraj eubiotik. LAB memberikan perlindungan melalui pelbagai mekanisme termasuk pengeluaran posbiotik. Salah satu gangguan utama yang menjejaskan kesihatan faraj ialah kandidiasis vulvovaginal (VVC) dan rekurensnya, disebabkan oleh spesis *Candida* termasuk *Candida albicans* dan *Candida glabrata*. Spesis *Candida*, terutamanya *C. albicans* ialah patogen penghasil biofilem dan lazimnya membentuk sebahagian daripada mikrobiota faraj. Penyelidikan terkini telah mengaitkan peranan biofilem kulat dalam VVC, terutamanya dalam aspek kegagalan rawatan dan berulang. Kajian ini bertujuan untuk menilai aktiviti antibiofilem postbiotik yang dihasilkan oleh *Limosilactobacillus reuteri* 29A, *in vitro* dan dalam model mencit VVC. Supernatan bebas sel (CFS) *L. reuteri* 29A diperoleh daripada kultur segar anerobik 48 jam *L. reuteri* 29A dalam media De Man, Rogosa dan Sharpe (MRS). Ia ditapis-sterilisasi sebelum diuji dalam biofilem prabentuk *C. albicans* (ATCC 14053), *C. glabrata* (ATCC 2001) stren rujukan dan *C. albicans* (S.21), *C. glabrata* (95670) stren klinikal. Khususnya, *L. reuteri* 29A CFS memusnahkan 91% daripada *C. albicans* ATCC 14053 dan 92% daripada biofilem *C. albicans* S.21. Untuk stren *C. glabrata*, *L. reuteri* 29A CFS menghalang 86% ATCC 2001 dan 83% untuk biofilem *C. glabrata* 95670. Mekanisme CFS bergantung pada tahap pH yang rendah. Metabolit yang dihasilkan dalam *L. reuteri* 29A CFS telah dikenalpasti menggunakan gas chromatography-mass spectrophotometry. Mikroskop electron pengimbas (SEM) memaparkan pemusnahan biofilem prabentuk dan halangan morfogenesis *C. albicans* selepas pentadbiran

posbiotik secara *in vitro*. Kajian ini juga bertujuan untuk mengkaji peranan CFS dalam model mencit VVC. Tikus betina BALB/c disuntik secara intravaginal dengan spesies klinikal *Candida* sebelum rawatan dengan *L. reuteri* 29A CFS. Pemeriksaan mikrobiologi dan pemeriksaan sitologi mendedahkan bahawa *C. albicans* pembentukan hifa kepada yis *C. albicans* telah dihalang selepas rawatan dengan *L. reuteri* 29A CFS. Pemeriksaan histopatologi mendedahkan pembentukan biofilem spesies *Candida* pada sel epitelia faraj. Walau bagaimanapun, selepas rawatan dengan *L. reuteri* 29A CFS, tisu faraj yang dijangkiti telah dipulihkan melalui perencatan biofilm spesies *Candida*. SEM dalam ujian *in vivo* selanjutnya memaparkan pengembalian semula mikroflora bakteria. Kiraan unit pembentuk koloni menunjukkan pengurangan beban kulat pada tikus yang dijangkiti selepas pentadbiran *L. reuteri* 29A CFS. Walaupun keberkesanan CFS *L. reuteri* 29A dibuktikan dalam ujikaji in vitro dan model mencit, limitasi kajian ini ialah aplikasinya ke atas subjek manusia. Secara keseluruhannya, keputusan kajian ini menunjukkan potensi penggunaan postbiotik *L. reuteri* 29A sebagai pilihan tambahan untuk merawat dan/atau mengelakkan jangkitan faraj oleh *Candida*.

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LIST OF ABBREVIATIONS

AIDS	Acquired immune deficiency syndrome
AMPs	Antimicrobial peptides
ANOVA	Analysis of variance
ATCC	American Type Culture Collection
AV	Aerobic vaginosis
BLF	Bovine lactoferrin
BV	Bacterial vaginosis
CDR1	*Candida* drug resistant gene 1
CFS	Cell free supernatant
ECM	Extracellular matrix
EPS	Extracellular polymeric substances
FLZ	Fluconazole
GC-MS	Gas Chromatography Mass Spectrophotometry
H_2O_2	Hydrogen peroxide
HIV	Human immunodeficiency virus
ILs	Interleukins
LAB	Lactic acid bacteria
MRS	De Man, Rogosa, Sharpe
NACS	Non-albicans *Candida* species
NaOH	Sodium hydroxide
OD_{600}	Optical density
OTC	Over the counter
PBS	Phosphate-buffered saline
PMN	Polymorphonuclear neutrophil
PRRs	Pattern recognition receptors
QS	Quorum sensing
QSMs	Quorum Sensing Molecules
RPM	Revolutions per minute
RPMI	Roswell Park Memorial Institute medium

RVVC	Recurrent vulvovaginal candidiasis
SDA	Sabouraud dextrose agar
SEM	Scanning electron microscopy
TV	Trichomonas vaginitis
VVC	Vulvovaginal candidiasis
YPD	Yeast extract-peptone-dextrose
^{o}C	degree celsius

CHAPTER 1

INTRODUCTION

Vaginal dysbiosis advocates burgeoning of devious human vaginal pathobionts like *Candida* species, that can churn out quorum sensing molecules that bind to receptors on immune cells and epithelial cell linings, rendering the host susceptible to infections. Inevitably, antifungal resistance emerges due to an adaptive technique like biofilm formation, which inflates fungal infiltration and persister cells formation. In consequence, the phenomenon of biofilm involvement in vulvovaginal candidiasis (VVC) and its recurrence has become paramount. The female vaginal territory houses a vast number of microorganisms with *Lactobacillus* species considered to be the most dominant microorganisms present (Ravel et al., 2011). In a normal vaginal microbiota of healthy women, there is cohabitation of both bacterial and fungal species existing in a regulated mutualistic relationship with the host. This is to keep the microbiota balanced, thereby keeping each other in check to avoid invasions leading to infections. The composition of the vaginal microbiota is said to be very dynamic and undergoes changes according to hormonal fluctuations throughout the woman's reproductive life. That is, from puberty to menopause, and also during pregnancy (Smith and Ravel, 2017). Studies show that the dominance or balance of *Lactobacillus* species provides a barrier against pathogens that are harmful to the vagina such as *Candida* species (Marchesi and Ravel, 2015). According to Amabebe and Anumbe (2018), the degree of protection conferred on the vaginal ecosystem is dependent on the predominance of *Lactobacillus* species (Amabebe and Anumba, 2018). *Lactobacillus* species are facultative anaerobe, gram-positive, catalase-negative, non-spore-forming rods and characterized by the production of lactic acid as end product. These along with other favourable metabolites gives superiority over other microorganisms in the host (Chew et al., 2015; Mokoena, 2017; Lourenço et al., 2019). One major mechanism of antagonism by *Lactobacillus* species is by the excretion of metabolites such as organic acids, amino acids, short chain fatty acids, reuterin, bacteriocins and biosurfactants to prevent pathogenic adherence and colonization (Cleusix et al., 2007; Ceresa et al., 2015; Satpute et al., 2016; Kobatake et al., 2017; Vieco-Saiz; Adu et al., 2020). This mechanism also gives lactic acid producing bacteria (LAB), competitive advantage over other microorganisms especially pathogens in the ecosystem such as *Candida* species.

Candida species, especially *Candida albicans* are widely known to be opportunistic pathogens that colonize mucosal surfaces and are mainly the cause of prevalent fungal species of the human microbiota (Mayer et al., 2013). *Candida* species are composed of a heterogeneous group of microorganisms and are natural habitants of a healthy normal microbiota of a human's gastrointestinal system, vagina, and mucosal surfaces and known for their massive indulgence in disease prevalence (Eggimann et al., 2003; Sardi et al., 2013). *Candida* species, most notably *C. albicans* are notorious and can exhibit virulence by attaching to medical devices including catheters and dental implants which provide a sanctuary for biofilm growth (Douglas, 2003). They have the ability to invade host organisms, adhere to surfaces and form biofilms which contribute to their pathogenicity (Ortega et al., 2011). *C. albicans* are asymptomatic in individuals until unfavourable factors such as changes in pH, immunosuppression, poor personal hygiene and even lifestyle cause an overgrowth of *C. albicans* leading to infections (Brown et al., 2014; Jabra-Rizk et al., 2016). Due to their clinical significance, researchers are recognizing the value of investigating their virulence through biofilm formation rather than their planktonic forms. Biofilms are a form of protective layer for most microorganisms and help to maintain the role of the fungi as a pathogen and giving it the ability to withstand harsh conditions such as competition from other microorganisms and also resist antifungal agents (Kuhn et al., 2002). Therefore, fungal biofilm formation play a major role in their pathogenesis. Biofilm-associated bacterial and fungal microorganisms have increasingly been recognized to play a role in multiple infectious diseases, particularly in their persistence and recurrence. More recently, biofilms have also been implicated in vaginal infections, notably bacterial vaginosis (BV) and vulvovaginal candidiasis (VVC), particularly in the setting of treatment failure and recurrence.

VVC, RVVC and BV are the most known infections threatening women health and have major impact on women health and well-being (Makanjuola et al., 2018; Rosati et al., 2020). These conditions are incidences of vaginal dysbiosis and mostly a result of the imbalance of *lactobacilli* presence in the vagina. Although *C. albicans* are the main causative agents of VVC, *non-albicans Candida* species (NACS), especially *C. glabrata* are receiving attention due to the major increase of their role in these infections. Around 10% to 20% of cases has been reported for this strain followed by other strains such as *C. krusei* and *C. parapsilosis* (Cetin et al., 2007). According to Cetin and colleagues in their study, NACS are more likely to be in favour of vaginal infection reoccurrence such as RVVC (Cetin et al., 2007). It is still unclear what contributes to the shift from VVC to RVVC, but studies indicate it is more severe than the latter. Therefore, it may be hypothesized that host’s immunological responses to antifungals, severity of the episodes of the infections, antimicrobial drug resistance and presence of persister cells can lead to reoccurrence of vaginal infections even after treatment. Over the years, *Candida* species have been able to form drug-resistant biofilms which have increased their effect in causing human diseases. Due to this increase in resistance of strains of *Candida* species, search for new target of antifungals are being investigated (Sardi et al., 2013). Mostly, studies conducted to investigate biofilm related infections have been done *in vitro.* However, only a few studies have been carried out on biofilms grown on the vaginal epithelium (Harriott et al., 2010; Peters et al., 2014).

The vaginal ecosystem is comprised of both anaerobic and aerobic microorganisms which have been grouped into five vaginal community state types (CSTs) (Gajer et al., 2012). Lactobacilli are the most abundant microorganisms isolated from vaginal CSTs of healthy women (Ravel et al., 2011). These lactobacilli species often defend the host against fungal colonization through competitive exclusion and production of antifungal metabolites (Matsubara et al.,2016; Fuochi et al., 2019; Wegh et al., 2019; Kalia et al., 2019), which gives them competitive advantage over other microorganisms in the polymicrobial environment (Maragkoudakis et al., 2010). These metabolites are generally termed as postbiotics and are plausible to aid in the health benefits of the probiotic strain (Matsumoto et al., 2011; Nataraj et al., 2020). Moreover, postbiotics are secondary metabolites (e.g., bacteriocins, organic acids, short chain fatty acids, biosurfactants, amino acids, peptides, EPS) which are excreted in the cell-free supernatants (CFS) of live probiotic microorganisms and are strain dependent. According to Wegh et al., 2019, postbiotics are defined as functional bioactive compounds generated in a matrix during fermentation, which may be used to promote health (Wegh et al., 2019). Postbiotics can imitate the beneficial therapeutic effects of probiotics while avoiding the risk of administering live microorganisms to the host (Taverniti at al., 2011). Thereby, postbiotics are generally considered as a safer treatment replacement in immunocompromised patients (e.g., pregnant women). Other benefits include longer shelf-life when compared to probiotics. Furthermore, postbiotics produced by LAB can generate hostile situations such as alterations in the acidic condition of the vaginal environment thereby affecting pathogenic microorganisms such as *Candida* species gravely and antagonizing their infections (Chew et al., 2015; Kim and Park, 2017; Meleh et al., 2020). Metabolites found in the reproductive tract play an important role in the female genital tract inflammation, pregnancy, and cancer (Ghartey et al., 2015; Song et al., 2019). Therefore, they are considered as biomarkers for disease prognosis, inflammation, and adverse pregnancy outcomes (Li et al., 2020).

The study hypothesis is that postbiotics produced by *Lactobacillus* species have adverse mechanisms and factors influencing their antagonism against *Candida* species *in vitro* and *in vivo*, and therefore necessary to study the related mechanisms. Additionally, the inhibitory effects of *Lactobacillus* strains to a greater extent, if not totally, is ascribed to non-bacteriocin metabolites secreted by probiotic strains into the growth media. The possibility that there is a combined synergistic effect between low pH and metabolites produced by *Lactobacillus* strains cannot be ruled out and therefore requires further studies. Hence, in this study, we aimed to evaluate the antibiofilm activities with postbiotics qualities by *Limosilactobacillus reuteri* 29A CFS against *C. albicans* and *C. glabrata in vitro* and *in vivo*.

Objectives

Main objective:

To investigate the antibiofilm effects of *Limosilactobacillus reuteri* 29A cell-free supernatant against *Candida* species and in murine model of vulvovaginal candidiasis

Specific objectives:

1. To elucidate the antibiofilm effects of *L. reuteri* 29A CFS against preformed biofilms of major *Candida* species *in vitro* and *in vivo*

2. To determine and identify factors influencing the antibiofilm potency of *L. reuteri* 29A CFS against preformed biofilms of *Candida* species *in vitro*

3. To determine the safety and efficacy of *L. reuteri* 29A CFS in murine model of vulvovaginal candidiasis

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