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The Antivirulence Mechanisms of Phytate Against Pathogenic Bacteria in Skin Infections

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Abstract

Skin infections caused by the bacteria *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Propionibacterium acnes* are often a common health problem. One treatment is antibiotics, but the cases of antibiotic resistance are increasing. Thus, new treatment alternatives are needed. This study aimed to analyze the molecular mechanism of phytate antivirulence against pathogenic bacteria of skin infection. This study used a bioinformatics approach involving analysis of phytate interactions with bacterial virulent proteins via STITCH, functional classification of proteins with VICMpred, and prediction of virulence properties using VirulentPred. B-cell and MHC epitopes were analyzed using IEDB, while protein subcellular location was determined through PSORTb. The results showed that phytate interacted specifically with virulent proteins in all three bacteria, most of which functioned in cellular and metabolic processes. These virulent proteins also have immunologically relevant epitopes. Subcellular location analysis showed that phytate protein targets were dispersed in the cytoplasmic membrane and cytoplasm. These findings indicated that phytate has a significant antivirulence mechanism by targeting virulent proteins of skin pathogenic bacteria, thus potentially becoming a therapeutic agent to treat skin infections while reducing antibiotic resistance.

Keywords: Phytate; Antivirulence; Staphylococcus aureus; Streptococcus pyogenes; Propionibacterium acnes.

INTRODUCTION

The skin can become infected because microorganisms can penetrate the damaged skin barrier. Skin infections can be caused by viruses, bacteria, fungi, or parasites (Lidjaja, 2022). Based on data from the Demographic Health Survey in Indonesia in 2016, the prevalence of skin diseases was 2.93% to 27.5% (Edison et al., 2023). According to the World Health Organization (WHO), the prevalence of infectious skin diseases in 2020 was reported to be around 300 million cases per year. The prevalence of skin diseases in Indonesia is 4.60%-12.95%, ranking third out of the top 10 diseases (Sri Rahayu et al., 2023). The bacteria *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Propionibacterium acnes* commonly cause skin infections.

Staphylococcus aureus, *Streptococcus pyogenes*, and *Propionibacterium acnes* are Gram-positive bacteria. *Staphylococcus aureus* is a spherical bacterium with a diameter of 0.7-1.2 μm, forms irregular groups resembling grapes, does not form spores, is facultatively anaerobic, and does not move (Devi et al., 2022). Then, *Streptococcus pyogenes* bacteria are cocci, arranged in chains, and show catalase and oxidase activity (Savitri et al., 2019). *Propionibacterium acnes* bacteria, on the other hand, belong to the Corynebacteria family but have no toxicity (Zahrah et al., 2018).

Antibiotic resistance is the ability of microorganisms to inhibit the action of antimicrobial agents, and this phenomenon occurs when antibiotics lose their efficiency in inhibiting bacterial growth, which is one of the most important public health problems to be solved (Putri et al., 2023). According to the Antimicrobial Resistance Control Committee, bacterial resistance in Indonesia continued to increase from 2013 to 2019 (Marsudi et al., 2021) and according to Suhartini in 2024, the prevalence of antibiotic use in Indonesia is in the high category, which is 40%-60% (Suhartini & Rahmi Makmur, 2024). Uncontrolled use of antibiotics causes resistance to increase. The wrong antibiotics can cause resistant bacteria (Lubis et al., 2019).

Phytate (chemically known as myoinositol (1,2,3,4,5,6) hexakisphosphate). Phytate in plants is a source of energy and antioxidant capacity (as a phosphate group donor) but has a major role as a candidate antimicrobial natural material (specifically Cu2+ and Zn2+ cation depots) due to its negative charge at physiological pH (Pires et al., 2023). In a

bioinformatics study conducted by Hashimoto et al (2022), it was shown that consuming phytate-enriched foods such as rice can induce an increase in epithelial antimicrobial defence mechanisms in the gut, protecting against infection by pathogenic bacteria such as *E. coli* (Hashimoto-Hill et al., 2022). Then in the study of Sorour et al (2022) they conducted research on the antibacterial properties of pure phytate compound extracts and showed that Gram-positive bacteria were more sensitive to phytate compounds than Gram-negative bacteria (Sorour et al., 2022)

MATERIALS AND METHODS

Type of Research

This study used a computational approach with bioinformatics methods that utilise data analysis as a method to explore and understand more about virulence factors in three types of pathogenic bacteria, namely *Staphylococcus aureus Mu50*, *Streptococcus Pyogenes M1 GAS*, and *Propionibacterium acnes KPA171202*.

Population and Sample

This study's samples were phytate and FASTA compounds from the protein sequences of *Staphylococcus aureus Mu50*, *Streptococcus Pyogenes M1 GAS*, and *Propionibacterium acnes KPA171202*.

Data Collection

STITCH version 5.0 was used as an interaction analysis of *Staphylococcus aureus Mu50*, *Streptococcus Pyogenes M1 GAS*, and *Propionibacterium acnes KPA171202* targeted to phytate compounds, then FASTA was downloaded from the National Center for Biotechnology Information (NCBI) database. FASTA files were downloaded and renamed according to the protein name of the bacteria targeted by phytate compounds. The FASTA was used in functional class analysis, virulence trait analysis, epitope analysis, and subcellular analysis of proteins from *Staphylococcus aureus Mu50*, *Streptococcus Pyogenes M1 GAS*, and *Propionibacterium acnes KPA171202* that interact with phytate compounds using VICMPred, VirulentPred, BepiPred version 2.0, MHC-I Binding Prediction, MHC-II Binding Prediction, and PSORTb version 3.0.

Data Analysis and Processing

Interaction Analysis of Compounds and Bacterial Proteins

Web STITCH version 5.0 accessible through http://stitch.embl.de was analyzed in relation to the interaction of compounds and bacteria *Staphylococcus aureus Mu50*, *Streptococcus pyogenes M1 GAS*, and *Propionibacterium acnes KPA171202* to see the interaction between protein sequences that interact with phytate compounds. The results of the analysis are in the form of a three-dimensional diagram. Then, the FASTA download of protein sequences through NCBI (National Center for Biotechnology Information) data was carried out to be used in the next stage of analysis.

Functional Class Analysis

Functional class analysis of the protein sequences of *Staphylococcus aureus Mu50*, *Streptococcus pyogenes M1 GAS*, and *Propionibacterium acnes KPA171202* bacteria was analyzed on the website http://crdd.osdd.net/raghava/vicmpred/

Virulence Trait Analysis

The VirulentPred 2.0 website https://bioinfo.icgeb.res.in/virulent2/ was employed to analyze the virulence properties of protein sequences targeted by phytate compounds.

B-cell Epitope Analysis

The IEDB Analysis Resource website accessible at http://tools.iedb.org/bcell/ was used for B cell epitope analysis.

MHC I Epitope Analysis

MHC I epitope analysis of protein sequences targeted by phytate using MHC I Binding Predictions accessible on the website http://tools.iedb.org/mhci/.

MHC II Epitope Analysis

MHC II epitope analysis of protein sequences targeted by phytate compounds using MHC I Binding Predictions accessible on the website http://tools.iedb.org/mhcii/.

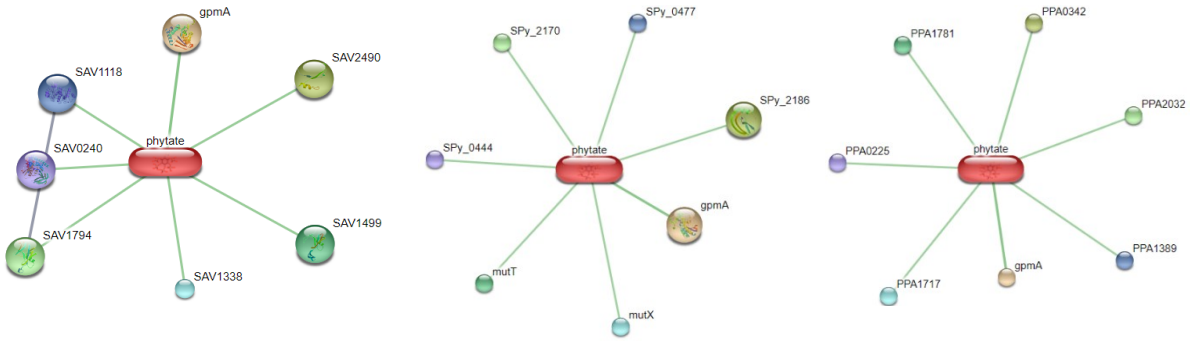
Subcellular Location Analysis

The PSORTb v3.0.3 website which can be accessed through https://www.psort.org/psortb/ was used to analyze the subcellular location of protein sequences.

RESULTS AND DISCUSSION

Interaction Analysis of Compounds and Bacterial Proteins

Analysis of protein interactions using STITCH version 5.0 shows several proteins from the interaction between *phytate compounds and Staphylococcus aureus Mu50, Streptococcus pyogenes M1 GAS,* and *Propionibacterium acnes KPA171202.* The analysis diagram is shown in Figure 1.



A B C

Figure 1. Phytate Interaction Diagram with (A) Staphylococcus aureus Mu50 (B) Streptococcus pyogenes M1 GAS (C) Propionibacterium acnes KPA171202.

Functional Class Analysis and Virulence Traits

In the next step, the protein was analyzed using VICMPred and VirulentPred v2.0, and the functional class and virulence properties of each protein were obtained, as shown in Table 1.

Table 1. Analysis of Functional Classes and Virulence Properties of Staphylococcus aureus Mu50, Streptococcus pyogenes M1 GAS and Propionibacterium acnes KPA171202 Proteins Interacting with Phytate.

Organism	Identification Code	Proteins That React with Phytate	Vicmpred Functional Class	Virulent Pred
Staphylococcus aureus mu50	gpmA	phosphoglyceromutase; Catalyzes the interconversion of 2-phosphoglycerate and 3-phosphoglycerate (By similarity)	Cellular process	Non-virulent
	SAV2490	mutator protein mutT	Metabolism molecule	Non-virulent
	SAV1499	ADP-ribose pyrophosphatase	Metabolism molecule	Non-virulent
	SAV1338	hypothetical protein	Cellular process	Virulent
	SAV1794	hypothetical protein	Information and Storage	Non-virulent
	SAV0240	flavohemoprotein	Cellular process	Non-virulent
	SAV1118	hypothetical protein	Information and Storage	Virulent
	gpmA	phosphoglyceromutase; Catalyzes the interconversion of 2-phosphoglycerate and 3-phosphoglycerate (By similarity)	**Cellular process**	non-virulent
Streptococcus pyogenes M1 GAS	SPy_2186	hypothetical protein	**Cellular process**	virulent
	Spy_0477	hypothetical protein	**Cellular process**	Non-virulent
	SPy_2170	hypothetical protein	**Cellular process**	virulent
	SPy_0444	hypothetical protein	**Metabolism Molecule**	Non-virulent
	mutT	protein mutator	**Information and Storage**	Non-virulent
	mutX	7,8-dihydro-8-oxoguanine-triphosphatase	**Cellular process**	Non-virulent
	gpmA	phosphoglyceromutase; Catalyzes the interconversion of 2-phosphoglycerate and 3-phosphoglycerate (By similarity)	**Cellular process**	Non-virulent
Propionibacterium acnes KPA171202	PPA1717	hypothetical protein	**Cellular process**	Non-virulent
	PPA0225	NTP pyrophosphohydrolase	**Metabolism Molecule**	virulent
	PPA1781	7,8-dihydro-8-oxoguanine-triphosphatase	**Cellular process**	Non-virulent
	PPA0342	hypothetical protein	**Metabolism Molecule**	Non-virulent
	PPA2032	MutT/NUDIX family proteins	**Cellular process**	virulent

B Cell Epitope Analysis

The analysis of B cell epitopes is a continuation of the study of functional classes and virulence properties of *Staphylococcus aureus Mu50*, *Streptococcus pyogenes M1 GAS*, and *Propionibacterium acnes KPA171202* proteins that interact with phytate compounds, in this

step using Bepipred with virulent proteins from each interaction. Analysis of each protein revealed the presence of amino acid sequences that can bind to B cells. The study results can be seen from the emergence of graphs with different colors: yellow and green. The yellow graph indicates an interaction between the protein compound and the B cell epitope. The result of Cell Epitops can be seen in Figure 2.

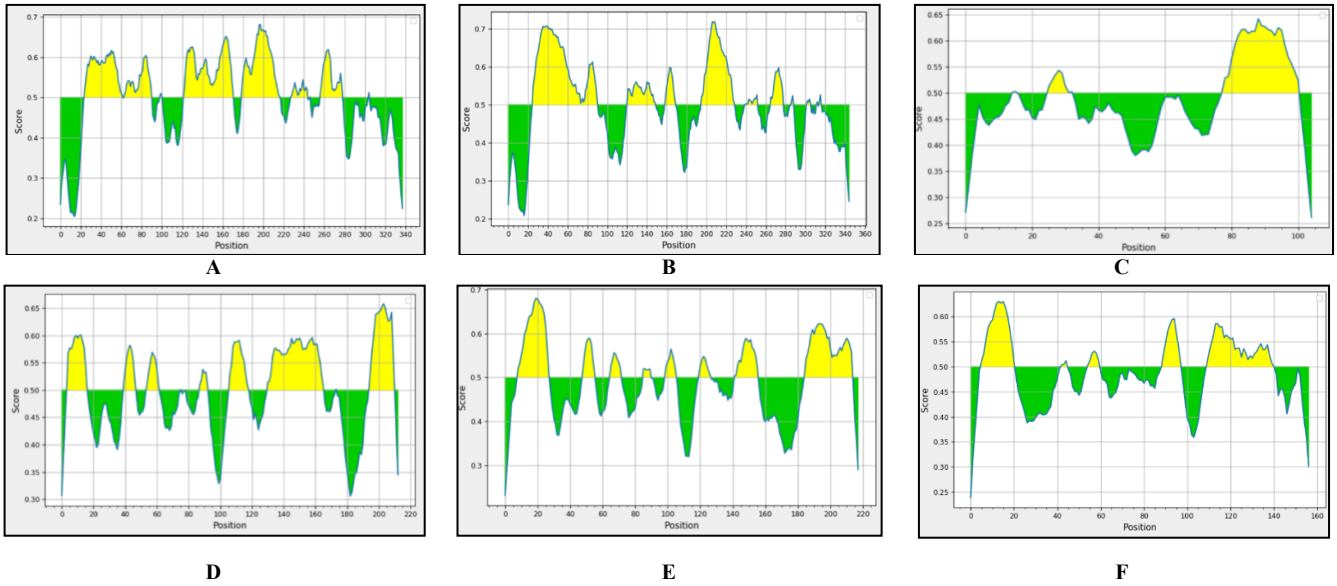


Figure 2. Result of B Cell Epitopes on (A) SAV1338, (B) SAV1118, (C) Spy_2186, (D) Spy_2170, (E) PPA0225, (F) PPA2032
Information :
a. Yellow peaks indicate sequences that have potential epitopes.
b. Green peaks indicate sequences that do not have potential epitopes.

MHC I and MHC II Analysis

The results of MHC I epitope prediction analysis using the HLA-A*11:01 allele with a peptide strand length of 9 amino acids. Moreover, MHC II epitope analysis, peptides with a length of 15 amino acids were identified using the HLA-DRB1*04:01 allele. The highest score indicates the potential for virulent bacterial proteins to bind to T cells. The resulting binding score also shows strong affinity, so there is a high potential for interaction between proteins and MHC I that allows recognition by T cells. All results are presented in tabular form, and the top five of all peptides with the highest score were taken. The results of the analysis are shown in Table 2 and Table 3.

Table 2. MHC I Analysis Results.

Protein	Allele	Start	End	Length	Peptides	Score	Percentile Rank
SAV1118	HLAA*11:01	141	149	9	SINPEPSFK	0.96	0.01
	HLAA*11:01	178	186	9	QVYSDQQSK	0.88	0.03
	HLAA*11:01	100	108	9	NSYYIVSTK	0.76	0.09
	HLAA*11:01	83	91	9	RVYPFRDGY	0.67	0.16
	HLAA*11:01	234	242	9	VTNEMRKLK	0.59	0.21
SAV1338	HLAA*11:01	16	24	9	IIAPITEFK	0.91	0.02
	HLAA*11:01	84	92	9	VTFNEYGTK	0.73	0.12
	HLAA*11:01	228	236	9	KQHQLSTLK	0.55	0.25
	HLAA*11:01	239	247	9	KQNSETARK	0.48	0.31
	HLAA*11:01	300	308	9	LMNSIGHRK	0.44	0.36
Spy_2170	HLAA*11:01	53	131	9	ILNDESIAK	0.53	0.26
	HLAA*11:01	59	67	9	LLFTDPVYY	0.21	0.85
	HLAA*11:01	9	17	9	QAKPLGEEK	0.11	1.3
	HLAA*11:01	50	58	9	KVFIVPLRQ	0.09	1.4
	HLAA*11:01	40	118	9	WGMTAQFTK	0.07	1.7
Spy_2186	HLAA*11:01	5	13	9	LVSPLEDPK	0.30	0.59
	HLAA*11:01	27	35	9	GFQSINWIK	0.05	2.0
	HLAA*11:01	22	30	9	GGTSLVGEK	0.02	2.9
	HLAA*11:01	30	38	9	KTHETVLRE	0.01	3.4

	HLAA*11:01	4	12	9	RNGKNFLTR	0.01	3.4
PPA0225	HLAA*11:01	35	43	9	HVLDALLDR	0.35	0.5
	HLAA*11:01	10	18	9	TTRHPSGYR	0.24	0.75
	HLAA*11:01	9	17	9	ATTRHPSGY	0.18	0.94
	HLAA*11:01	5	13	9	SALIASLGR	0.17	0.96
	HLAA*11:01	45	53	9	LTRRPLSLR	0.11	1.3
PPA2032	HLAA*11:01	35	43	9	RTCLNVRKK	0.44	0.36
	HLAA*11:01	5	13	9	LVLDPDDLK	0.34	0.52
	HLAA*11:01	9	17	9	VTWRDGSGR	0.20	0.88
	HLAA*11:01	4	12	9	SVQCVVTWR	0.18	0.94
	HLAA*11:01	76	84	9	RVIPALQQQ	0.13	1.2

Table 3. MHC II Analysis Result.

Protein	Allele	Start	End	Length	Peptide	Score	Percentile Rank
SAV1118	HLA-DRB1*04:01	202	216	15	IEPYQLNSNSTSEEH	0.90	0.20
	HLA-DRB1*04:01	173	187	15	GDIYAQVYSDQQSKK	0.89	0.20
	HLA-DRB1*04:01	201	215	15	DIEPYQLNSNSTSEE	0.87	0.28
	HLA-DRB1*04:01	172	186	15	YGDIYAQVYSDQQSK	0.82	0.53
	HLA-DRB1*04:01	99	113	15	KNSYYIVSTKREEIV	0.81	0.60
SAV1338	HLA-DRB1*04:01	234	248	15	TLKYSKQNSETARKH	0.90	0.20
	HLA-DRB1*04:01	233	247	15	STLKYSKQNSETARK	0.87	0.28
	HLA-DRB1*04:01	152	166	15	KGRVRYEQNNKEYDV	0.85	0.33
	HLA-DRB1*04:01	151	165	15	VKGRVRYEQNNKEYD	0.82	0.49
	HLA-DRB1*04:01	235	249	15	LKYSKQNSETARKHS	0.73	1.20
Spy_2170	HLA-DRB1*04:01	134	148	15	PVYYRLEVTPIETTD	0.93	0.13
	HLA-DRB1*04:01	133	147	15	DPVYYRLEVTPIETT	0.87	0.26
	HLA-DRB1*04:01	132	146	15	TDPVYYRLEVTPIET	0.76	0.96
	HLA-DRB1*04:01	135	149	15	VYYRLEVTPIETTDF	0.71	1.30
	HLA-DRB1*04:01	106	120	15	VDDWKSIQPNEEVDK	0.71	1.40
Spy_2186	HLA-DRB1*04:01	69	83	15	NIEFHYLVSPLEDPK	0.87	0.28
	HLA-DRB1*04:01	68	82	15	HNIEFHYLVSPLEDP	0.79	0.79
	HLA-DRB1*04:01	70	84	15	IEFHYLVSPLEDPKL	0.67	1.60
	HLA-DRB1*04:01	81	95	15	DPKLEMIENASDRFV	0.64	1.80
	HLA-DRB1*04:01	80	94	15	EDPKLEMIENASDRF	0.61	1.90
PPA0225	HLA-DRB1*04:01	136	150	15	RVRLADLANPAARAT	0.65	1.70
	HLA-DRB1*04:01	135	149	15	QRVRLADLANPAARA	0.62	1.90
	HLA-DRB1*04:01	134	148	15	VQRVRLADLANPAAR	0.43	3.90
	HLA-DRB1*04:01	28	42	15	RSSAVLALISEEGND	0.35	5.30
	HLA-DRB1*04:01	29	43	15	SSAVLALISEEGNDI	0.32	5.80
PPA2032	HLA-DRB1*04:01	79	93	15	PDDLKHLGTFDAPAA	0.48	3.20
	HLA-DRB1*04:01	78	92	15	DPDDLKHLGTFDAPA	0.38	4.60
	HLA-DRB1*04:01	109	123	15	WREIWPEPVPDSEIV	0.38	4.70
	HLA-DRB1*04:01	108	122	15	NWREIWPEPVPDSEI	0.33	5.70
	HLA-DRB1*04:01	52	66	15	GGKIELGETPLEAAI	0.32	5.80

Next, the subcellular location of each virulent protein was analyzed using PSORTB. The results of the study are shown in Table 4.

Table 4. Subcellular Location Analysis Results.

Organism	Identification Code	Protein Name	Subcellular Location
Staphylococcus aureus Mu50	SAV1338	Hypothetical protein	Unknown
	SAV1118	Hypothetical protein	Unknown
Streptococcus pyogenes M1 GAS	SPy_2186	Hypothetical protein	Cytoplasmic
	SPy_2170	Hypothetical protein	Cytoplasmic
Propionibacterium acnes KPA171202	PPA0225	NTP pyrophosphohydrolase	Cytoplasmic membrane
	PPA2032	MutT/NUDIX family protein	Cytoplasmic

DISCUSSION

In the *Staphylococcus aureus Mu50*, the identified proteins include gpmA, SAV2490, SAV1499, SAV1338, SAV1794, SAV0240, and SAV1118. Meanwhile, in *Streptococcus pyogenes M1 GAS,* the proteins involved were SPy_0477, SPy_2186, gpmA, mutX, mutT, SPy_0444, and SPy_2170. Whereas in

Propionibacterium acnes KPA171202, the proteins involved include PPA0342, PPA2032, PPA1389, gpmA, PPA1717, PPA0225, and PPA1781. In the *Staphylococcus aureus* Mu50 strain, there is a close relationship between SAV1794, SAV0240, and SAV1118 proteins. According to the theory proposed by Pevsner, interactions between proteins usually occur between proteins with similar functions or structures. This strengthens the possibility that this group of proteins forms a specific functional network that can be disrupted by interactions with phytate compounds (Abdullah et al., 2022).

Based on the results, most of the proteins from the three bacteria had major functions in cellular processes and the metabolism of molecules. Proteins such as gpmA found in all three bacterial strains were known to play an important role in the glycolytic pathway. In addition, some proteins were also categorized in the information and storage function, which is related to genetic regulation and biological information storage mechanisms.

Phytate can interfere with bacterial metabolic pathways by binding and removing essential metals that support bacterial survival and proliferation. In bioinformatics studies of skin pathogens, phytate was found to interact with several specific proteins in *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Propionibacterium acnes*. Phytate not only functions as an antioxidant and anti-inflammatory agent but also as an antivirulence agent that intervenes in the metabolic pathways of bacteria. By binding to key proteins in energy metabolism and virulence, phytate can weaken the ability of bacteria to survive and cause infection (Pires et al., 2023a).

The next analysis looked at the virulent properties of each protein and only had two proteins that had virulent properties, namely: SAV 1338, SAV1118 (Staphylococcus aureus Mu50), SPy_2186, Spy_2170 (Streptococcus pyogenes), and PPA0225, PPA2032 (Propionibacterium acnes KPA171202). This is in line with research conducted by Yamazaki et al, where proteins in *Staphylococcus aureus* play a role in pathogenesis by regulating immune evasion mechanisms and facilitating biofilm formation, which facilitates infection and bacterial immunity to antibiotic therapy (Yamazaki et al., 2024). Phytate has the potential to interact with these virulent proteins, thereby inhibiting metabolic processes that are essential for bacterial survival. This indicates that phytate has the potential to be an antivirulence agent that can reduce the virulence of bacteria such as *Streptococcus pyogenes*.(Pires et al., 2023b)

B cell epitopes are segments of antigens recognized by antibodies in the immune system, and epitope analysis can identify specific regions on proteins that can trigger humoral immune responses (Sun et al., 2024). The analysis showed various peptide strands that can trigger immune responses, with a length of up to 66 amino acids in some proteins, such as SAV1338 and SAV1118. It is in line with previous studies where epitopes on *Staphylococcus aureus*, *Streptococcus pyogenes* and *Propionibacterium acnes* can be effective targets in the development of antibody-based vaccines (Ozberk et al., 2018).

Major Histocompatibility Complex (MHC)-related analysis consisting of two classes: MHC I binding predictions and MHC II binding predictions of virulent proteins. Peptides, or epitopes, are expressed on the surface of nucleated cells by Major Histocompatibility Complex (MHC) molecules in T cells. A key requirement for T cell activation is molecular recognition between the T cell receptor (TCR) expressed on the T cell surface and the peptide-MHC complex (pMHC) described on the surface of other cells. Without T-cell activation, an immune response cannot be mounted and initiated. A mechanism known as central tolerance is responsible for this process (Schaap-Johansen et al., 2021). The results of the MHC epitope analysis presented in Table 2 and Table 3 show that the six proteins derived from the three pathogenic bacteria have strong binding affinities to MHC I and MHC II.

MHC I presents itself as an antigen and induces CD8+ T cells, while MHC II presents itself as an antigen and induces CD4+ T cells. After being induced, the cytotoxic antigen-specific immune system of T cells was mediated by the activity of CD8+ T cells, and B cells became B cell memory due to the activity of CD4+ T cells. The combination of the two mechanisms formed antibodies that damage spike proteins so that an adaptive immune system is formed to fight bacteria (Suzana et al., 2022).

As described in previous studies, the activation of CD8+ and CD4+ T cells has an important role in fighting bacterial infections, where CD4+ T cells facilitate the production of antibodies by B cells (Shepherd & McLaren, 2020). The interaction between MHC and antigen epitopes on the surface of T cells is essential to enhance the effectiveness of immune responses, which suggests that phytate through its ability to intervene in bacterial metabolic pathways and enhance antigen binding, may play a role in enhancing immune responses to bacterial infections.

Subsequently, the subcellular location of the proteins with virulence properties was analyzed using PSORTb. Of most of the six proteins, three proteins were located in the cytoplasmic membrane (SPy_2186, SPy_2170, and PPA2032), one was located in the cytoplasmic membrane (PPA0225), and there were two proteins from *Staphylococcus aureus* Mu50 that were targeted by phytate compounds, the exact location of the subcellular location was not found.

CONCLUSION

This bioinformatics study on the antivirulence mechanism of phytate against *Staphylococcus aureus* strain Mu50, *Streptococcus pyogenes* M1 GAS, and *Propionibacterium acnes* strain KPA171202 reveals that phytate interacts molecularly with virulent proteins in these pathogenic bacteria. Functional analysis showed that these proteins are primarily involved in cellular processes and metabolic functions, with additional roles in information and storage for *Staphylococcus aureus* and *Streptococcus pyogenes*.

Epitopic analysis revealed the presence of B-cell epitopes and peptide strands with T-cell affinity. At the same time, subcellular localization placed virulent proteins in the cytoplasm for *Streptococcus pyogenes* and in the cytoplasmic membrane and cytoplasm for *Propionibacterium acnes*. However, localization for *Staphylococcus aureus* remains unconfirmed. Further experimental validation in the laboratory to confirm these findings is recommended, alongside additional research into the virulence factors of phytate and its effects on other pathogenic bacteria and compounds in rice.

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