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Establishing the Therapeutic Potential of Berberine Against the pyrC Gene of *Clavibacter michiganensis* Responsible for Causing Ring Rot Disease in Potatoes using Computational Approaches

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Abstract

Potatoes (*Solanum tuberosum*) are one of the most important food crops. Originating in the South American Andes, it is the fourth-largest food crop in the world after rice, wheat, and maize. They are used both in processed meals and by the food industry in preparing a range of different dishes. Therefore, in this study, we aim to examine different approaches for treating the bacterial diseases of potatoes, especially ring rot disease caused by the pathogen *Clavibacter michiganensis* subsp. Sepedonicus. As the disease progresses, outward cracking and internal decay of the infected tubers may also be observed. The causative genes of *Clavibacter michiganensis* subsp. Sepedonicus were retrieved from the Microbial Genome Database (MBGD). These genes were used for the construction of a protein-protein interaction network for the identification of hub genes using 12 different parameters on Cytohubba. The pyrC gene was identified as the key gene playing an important role in ring rot disease, which codes for Dihydroorotase. A list of antibacterial phytochemicals was collected through a literature study, followed by screening based on Lipinski's rule of 5 using ADMETLAB3.0. Further, the molecular docking studies between the 'pyrC' gene and screened phytochemicals revealed the therapeutic potential of berberine against potato bacterial disease ring rot. Berberine is one of the alkaloids. It is an organic product extracted from several different plants, including Oregon grape, barberry, and goldenseal. Berberine belongs to the isoquinoline alkaloide chemical class.

Keywords: Berberine, *Clavibacter michiganensis* subsp. Sepedonicus, Potato, pyrC, Ring Rot Disease

1. Introduction

Potato is known scientifically as *Solanum tuberosum*, which is a staple food crop ranked high. Concerning its economic value, nutritional value, and versatility. Potatoes are actually native to the South Andean region of South America, and their cultivation started about 7,000 years ago[1]. It is from these that they derived their tuberous underground stems, which primarily store carbohydrates, mainly in the form of starch[2]. Thus, cultivation primarily involves the utilisation of tubers as opposed to seeds; however, the morphology and physical features of the plant include compound leaves as well as flowers characteristic of the Solanaceae family. According to Hawkes[3], potatoes can vary in size, shape and colour, including those that are presumably alike. The round white potato is followed by small fingerling potatoes, to defensive small purple potatoes. Potatoes consist of many

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nutrients, and their chief constituent is carbohydrates, of which more than ninety five cent is starch, which is energy-giving. It also provides the other dietary facet for the same reason, since other bits like the B-complex Vitamins and Vitamin C, magnesium and potassium are also contained in them[4]. Potatoes can be grown in so many climates, and they give a large yield per hectare, which makes them central in providing food to the global population[5]. Supported nutritionally in many preparations in culinary practices, they are incorporating parts of the fundamental diets in lots of countries, underlining flexibility and the vital necessity of the bulbs in the diets all over the world[6]. To increase the yield of crops, an increase in disease resistance as well as the quality of nutrition, some of the activities being undertaken include research on genetics, breeding and agronomy of potatoes. Such measures are helpful when it comes to addressing issues as diverse as climate change effects, elevating the global population's demand for food, among others[7]. The first centre of origin of potatoes was the Andes, particularly in the region of Lake Titicaca. Historically, records show that the use of potatoes started as early as 8000 BCE, when there was the cultivation of the tuber. During the 15th and 16th centuries, the Inca civilisation had a highly flourishing economy and developed an innovative way of producing potatoes like Chuño or freeze-drying to preserve the potatoes for future use[8]. When potatoes arrived in Europe, no one had much trust in them. These women were considered to be deadly or bad because they were not included in the Bible, grew beneath the ground and were nightshades[9]. Important bacterial ailments have played an important role in the history of potato farming all over the world. In this case, bacterial infections have been a persistent vice for farmers and scholars since the time when the potato was first domesticated two thousand years ago in South America. These illnesses have impacted the farming techniques, international relations over trade, and research, as well as the yields and quality of produce. However, due to the emergence of Microbiology as a scientific discipline towards the end of the 1800, the studies on bacterial infections in potatoes were conducted seriously. Since then, there has been a great improvement in the knowledge of these infections, which has benefited disease resistance breeding programs, management strategies, and diagnostic methods.

The bacterial Infections set out to be the most dangerous problem in potato farming. The psychological effect is huge because they play a major role in food security, and therefore, they are a threat to all people worldwide. There is evidence of the effects of these diseases on trade rules, research targets, and field practice over time. The impacts are broad, being one among the seed tuber in the field and to the levels of storage[10]. The whole history of the development of plant pathology and microbiology is in many places related to the history of bacterial infections of the potato. To be precise with the origins, prevalence, and treatment of most of these problems, our understanding has undergone a big change; the major part of the problems started to be described at the end of the 19th century[11]. The rise of technology in disease-resistant cultivars, molecular pathogen characterisation, and detection has course this progress. The management of bacterial infections in potatoes has become more and more complicated because of the fact that the potato trade takes place all over the world, which mandates international collaboration in phytosanitary measures and disease control strategies[12]. Furthermore, climate change adds an additional layer of complexity, as it may change the prevalence and strengthen those illnesses[13]. The most important ones in terms of economic impact are ring rot (*Clavibacter michiganensis* subsp. Sepedonicus), blackleg and soft rot (Pectobacterium and Dickeya species), bacterial wilt (*Ralstonia solanacearum*), and common scab (Streptomyces species)[14]. Due to lower yield, deteriorated tuber quality, and seed lot rejection, these diseases may result in crop losses.

One of the most biotic barriers to potato production is bacterial illness, which is particularly prevalent in tropical and subtropical areas as well as some warm temperate regions of the world[15]. Worldwide, potatoes are afflicted by roughly seven bacterial illnesses that severely harm the plant's tubers, which are its most valuable component commercially[16]. According to Elphinstone[17], bacterial wilt and blackleg are the two most serious illnesses, whereas potato ring rot, pink eye, and common scab are the less serious ones. Potato bacterial infections continue to be a major global health concern. Bacterial infections cost farmers millions of dollars every year. Due to their significant impact on seed potato output and significant knock-on consequences on commerce, bacterial wilt, soft rot, and ring rot have drawn attention from around the world[18]. The ring rot illness that is being discussed is brought on by *Clavibacter michiganensis* subsp. Sepedonic. It was first identified following an epidemic in Germany in 1905[19], and it is one of the few significant plant infections that did not originate in the Andean South American

region where the crop originated. Due to the mobility in commerce of contaminated seed potato tubers, it was first discovered in Quebec, Canada, in 1931, and by 1940 it had spread to all significant potato-producing districts in both Canada and the USA. In total, this disease has only been recorded once in Mexico, but it frequently occurs in cold regions of North America with time gaps, north of the USA and Canada. In addition, cases of wilting and tuber rotting are rare, especially in the fields and stores with modern seed certification. A lack of enough seed potatoes is caused by ring rot that affects their quantity and trade.

2. Methodology

2.1 Protein Identification

A cross-species query at various parameters such as MCC, DMNC, MNC, DEGREE, EPC, Bottleneck, EcCentricity, Closeness, Radiality, *etc.*, is performed using cytoHubba to construct a STRING network between *Clavibacter michiganensis* subsp. Sepedonicus and *Solanum tuberosum*. Hub genes and their corresponding protein sequences were found by evaluating the resulting protein interaction network using Cytoscape software.

2.1.1 Modelling of Protein

Using the SWISS-MODEL program, we generated three-dimensional protein structures with the protein sequences downloaded from Cytoscape. Their PDB architecture was downloaded and used for further investigation.

2.1.2 Preparation of Library

Literature was prospected for phytochemicals with possible antiviral activities. 29 libraries of antibacterial phytochemicals were generated, and their canonical SMILES, names, and sources were downloaded from PubChem.

2.1.3 Virtual Screening

Screening of phytochemicals with ADMET Lab, following five recommendations by Lipinski, was done to generate a library of potential lead compounds. Thereafter, virtual screening was employed in searching for phytochemicals with advantageous pharmacokinetic and pharmacodynamic features.

2.1.4 Molecular Docking

Using molecular docking with Seamdock, we estimated the binding affinity of phytochemicals that were identified in Step 4, taking the protein structure predicted in Step 2 as the target protein. The molecular docking study was undertaken to identify the lead molecules. The modified parameters in the Autodock software used to obtain an appropriate model to correctly predict legend-protein interaction in Seamdock are mode number = 10, energy range = 5, exhaustiveness = 8, and spacing = 0.375.

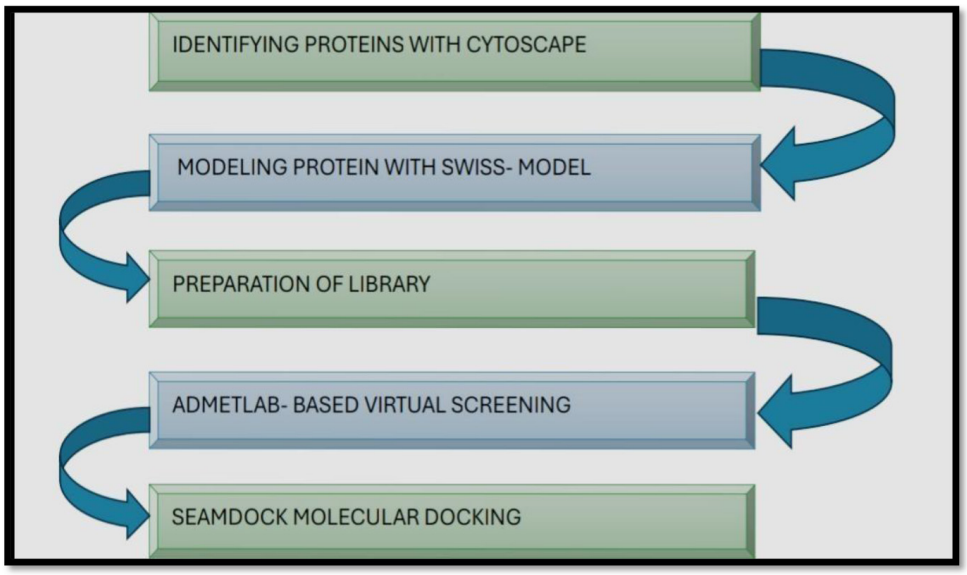


Figure 1. Flowchart representing the complete methodology opted in the present research.

3. Results and Discussion

3.1 Identification of Protein

We used 12 different parameters: MCC, DMNC, MNC, DEGREE, EPC, Bottleneck, EcCentricity, Closeness, Radiality, Betweenness, and stress for network analysis in cytoscape and cytohubba. We found, using the top 20 genes at a confidence level of 0.4, that the "pyrC" gene was the priority gene (Table 1, Figures 2-13).

3.2 Protein Modelling

SWISS-MODEL: Take the protein sequences obtained in Cytoscape and generate their 3D protein structures.

'pyrC' protein sequence

Table 1. The different genes at different parameters

mcc	dmnc	mnc	Degree	epc	Bottleneck	EcCentricity	Radiality	Closeness	Betweeness	Stress	Clustering coefficient
pyrC	pyrC	carB	pyrC	pyrC	pyrC	carB	pyrC	pyrC	pyrC	aspA	pyrC
rpIV	rpIV	pyrC	rpIV	rpIV	rpIV	pyrC	rpIV	rpIV	rsIV	carB	rpIV
carB	aspA	rpIV	carB	carB	carB	rpIV	carB	carB	carB	proC	aspA
rpsH	rpsH	rpoC	rpsH	rpsH	rpsH	rpoC	rpsH	rpsH	rpsH	pyrC	rpsH
rpoC	rpoC	rpsH	rpoC	rpoC	rpoC	rpsH	rpoC	rpoC	rpoC	rpIV	rpoC

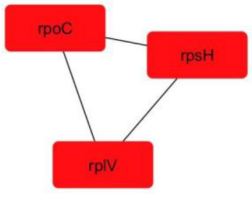


Figure 2. MCC.

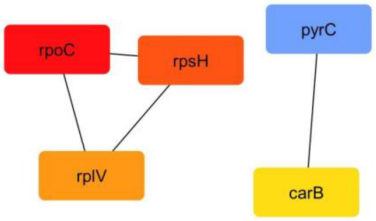


Figure 3. EPC.

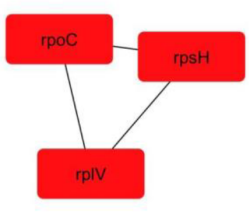


Figure 4. Radiality.

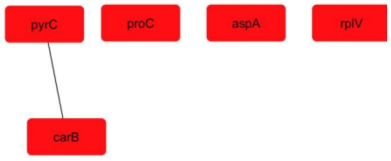


Figure 5. Stress.

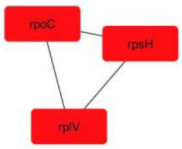


Figure 6. DMNC.

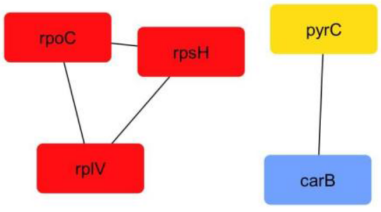


Figure 7. EcCentricity.

Figures 2-13. The result obtained from a string network in cytoscape using 12 parameters.

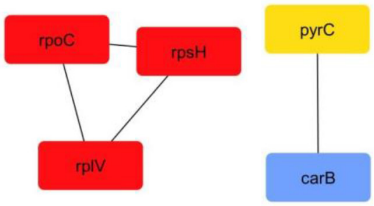


Figure 8. Closeness.

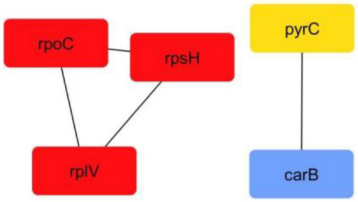


Figure 9. Degree.

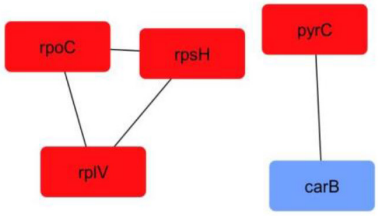


Figure 10. Bottleneck.

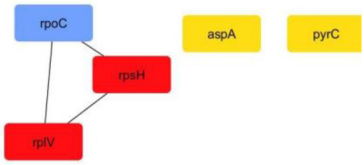
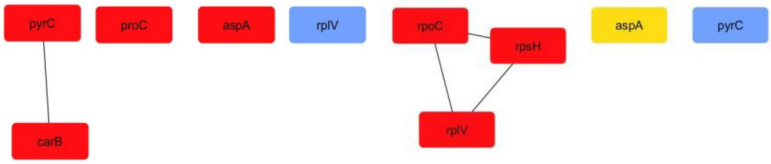


Figure 11. Clustering coefficient.



Figures 2-13. Continued...

AELRCKEKILANKTRTFTAAPLDTLLGGKVCVD
DFNNQFYSKNIECCWTVGMTKFY
GGWDKLLRRLPENWVYCDADGSQFDSSLTPYL
INAVLTIRSTYMEDWDVGLQMLRV
LYTEIVYTPISTPDGTIVKKFRGNNSGQPSTVVD
NSLMVVLAMHYALIKECVEFEEIDS
TCVFFVNGDDLLIAVNPEKESILDRMSQHFSDLG
LNYDFSSRTRRKEELWFMSHRGL
LIEGMYVPKLEEERIVSILQWDRADLPEHRLEAIC
AAMIESWGYSELTHQIRRFYSWL
LQQQPFATIAQEGKAPYIASMALRKLYMDRAVD
EEELRAFTEMMVALDDEFELDSYE
VHHQAKHSAWMFEALTGNLQAVATMKSQLVTK
HVVKGECRHFTEFLTVDAEAEAE
AFFRPLMDAYGKSLLNRDAYIKDIMKYSKPIDVG
VVDRMHLRKPSIGLSSTCNVHGF
KKCAYVTDEQEIFKALNMKAAVGASYGCKKKD
YFEHFTDADKEEIVMQSCLRLYK
GLLGIWNG

4. Preparation of Library and Virtual Screening

A library of 29 compounds was produced by listing the antiviral phytochemicals identified by PubChem and the

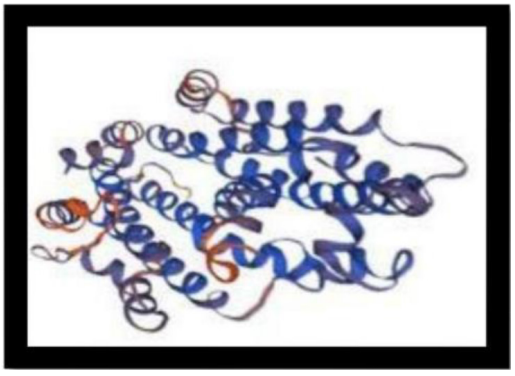


Figure 14. 3D protein structure of pyrC gene, generated by SWISS-MODEL.

literature review, the names and sources, along with the canonical SMILES.

ADMET Lab and Lipinski's Rule of Five. The phytochemicals were screened for the respective attributes. Lipinski's rule of five using ADMETLab 3.0; 29 antiviral phytocompounds follow Lipinski's rule of five. The table representation of phytochemicals with Lipinski's rule shows accepted or rejected (Table 2).

5. Molecular Docking

Seam Dock Docking: Based on molecular docking experiments between the screened phytochemicals and the 3D protein structure of the "pyrC" gene, "berberine" has shown strong therapeutic promise against *Clavibacter michiganensis* subsp. Sepedonicus. The infected berberine may be a powerful drug against antibacterial medication because of its relevantly significant binding affinity for the "pyrC" protein in the docking tests. Berberine is the phytochemical that holds the lowest binding energy (-7.15) and the highest binding affinity towards the structure of bacterial proteins.

6. Discussion

This research demonstrates an innovative approach to combating potato ring rot disease caused by *Clavibacter michiganensis* subsp. Sepedonicus[20]. By integrating bioinformatics, molecular modelling, and virtual screening techniques, the study identified the pyrC gene as a key factor in the disease process and pinpointed conessine as a promising plant-derived antimicrobial compound[21]. The use

Table 2. List of phytochemicals, along with the Lipinski rule, accepted or rejected

Antibacterial phytochemical	Sources	Lipinski rule
Allicin	*Allium sativum, Allium* spp.	Accepted
Conessine	*Holarrhena floribunda, Holarrhena antidysenterica, Funtumia elastica*	Accepted
Thymol	*Thymus vulgaris, Thymus capitatus*	Accepted
Carvacrol	*Origanum vulgare*	Accepted
Eugenol	*Syzygium aromaticum, Eugenia caryophyllus*	Accepted
Berberine	*Berberis vulgaris, Berberis fremontii, Hydrastis canadensis*	Accepted
Curcumin I	*Curcuma longa*	Accepted
Quercetin	*Capparis spinosa, Polymnia fruticose, Ginkgo biloba*	Accepted
Epigallocatechin	*Camellia sinensis*	Accepted
Catechin	*Fructus crataegi*	Accepted
Genistein	*Glycine max*	Accepted
Protocatechuic acid	*Scrophularia frutescens*	Accepted
Gallic acid	*Vitis rotundifolia*	Accepted
Hydroquinone	*Vaccinium myrtilles*	Accepted
Osthole	*Cnidium monnieri, Angelica archangelica. Angeliat pubescens*	Accepted
Taxifolin	*Silybum marianum, Allium cepo, Prendetsuga taxifolia, Pinus pinauter*	Accepted
Piperine	*Piper nigrum*	Accepted
Sophoraflavanone	*Desmodison caudatum*	Accepted
Farnesol	*Vachellia furnesiana*	Accepted
Ellagic acid	*Rosa rugosa*	Accepted
Chebulagic acid	*Terminalia chebula*	Rejected
Chlorogenic acid	Fruits, vegetables, and graminaceous plants	Accepted
Thymoquinone	*Nigella sativa*	Accepted
Guggulsterone	*Commiphora wightii* (Am) Ilhandar	Accepted
Isoliquiritigenin	*Glycyrrhiza uralensis*	Accepted
Celastrol	*Tripterygium wilfordii*	Accepted
Cryptotanshinone	*Salvia miltiorrhiza* Bunge	Accepted
Oridonin	*Rabdasia rubescens, Loden rubescens*	Accepted
Magnolol	*Magnolia officinalis*	Accepted

Table 3. List of phytochemicals and their amino acid residues and binding energy between Phytochemicals and the protein of pyrC gene

Antibacterial phytochemical	Binding energy	Amino acid residues
Allicin	-4.17	F90,R121,V148,V150,L366,A146, P122
Thymol	-1.13	L59,H60,I123,V150,V177,A179,H231,I363
Carvacrol	-6.35	F90, A147, R149, V150, L366,P122
Eugenol	-5.01	F90,R121,L366,A146,R149,V150,P122,V148
Berberine	-7.15	D396,L83(A),R414,V415,E331,D395,D396,G84
Curcumin I	-5.58	L83,D396,R414,L431,D395,D396,G398,R390,V415,E331
Quercetin	-6.9	A275,R276,K316,N403,D274,H311,P312,T313,G402,
Epigallocatechi n	-6.59	F90,R121,A147,R149,R365,P122,A146,V150,
Catechin	56.59	L59,F86,P260,V303,A305,T306,A333,P360,E257,V355,M356,V57,V304,V 305,D58
Genistein	86.67	L56,L59,F86,V303,A305,A333,M356,P360,G84,V57,
Protocatechuic acid	-6.04	R121,F90,R149,P122,A146,A147,V150,V148
Gallic acid	1.39	L59,I123,V150,A179,H231,H60,C233,G364
Hydroquinone	-5.15	F90,R121,R149,A146,G364
Osthole	36.91	L59,F86,P260,V303,V304,T306,A333,P360,E257,V57,M356,D58
Taxifolin	114.26	L59,H60,V150,A179,A305,P360,V57,D58,C233,E257,V355,
Piperine	31.96	L59,H60,I123,V150,A179,E257,V303,A305,M356,P360,F86,E257,H231,
Sophoraflavanone	145.94	D154,L59,H60,F90,V150,A179,E257,V303,I363,H231,H60,S152,C233,E2 57,M92
Farnesol	30.55	L59,F86,P260,V303,V304,A305,T306,A333,V336,P360,T259,V337
Ellagic acid	170.1	I363,H231,E257,S152
Chlorogenic acid	39.71	H231,L59,V150,V303,A305,P360,C233,E257,M356,H60,D58,G364
Thymoquinone	-0.2	L59,H60,I123,V150,V177,A179,H231,I363
Guggulsterone	206.85	D58,F86,V303,V304,T306,A333,V337,A305
Isoliquiritigenin	30.91	L59,H60,V150,A179,E257,V303,A305,P360
Celastrol	836.11	L56,F86,P260,V304,T306,L330,A333,M356,V57,V304,M327,V328,S332,V 355,V304
Cryptotanshino ne	191.14	L59,F86,V303,P360,H231
Oridonin	279.1	L59,H60,F90,V150,I363,C233,H231
Magnolol	66.79	L59,H60, I123,V150,D154,V177,A179,I363,H231,E257

of cross-species network analysis to identify the pyrC gene highlights the power of systems biology in understanding pathogen-host interactions[22]. The subsequent protein modelling and virtual screening of phytochemicals showcase the efficiency of in silico methods in drug discovery, significantly streamlining the initial screening process[23]. The Identification of berberine as the compound with the highest binding affinity to the pyrC protein suggests its potential as an effective biopesticide[24]. This finding underscores the value of natural products as sources of novel antimicrobial agents and offers a promising lead for developing sustainable solutions to protect potato crops[25]. However, while these computational results are encouraging, experimental validation through in vitro and in vivo studies is crucial to confirm berberine efficacy and safety[26]. The study's focused approach on a single pathogen-host interaction, while thorough, may limit its broader applicability[27]. Overall, this multidisciplinary approach represents a significant step forward in addressing agricultural challenges, potentially leading to more targeted and efficient development of plant-based antimicrobial agents[28]. As global food security faces increasing threats from climate change and evolving pathogens, such innovative strategies for crop protection become increasingly valuable[29].

7. Conclusion

This research focused on the identification of plant-derived antimicrobial compounds against *Clavibacter michiganensis* subsp. Sepedonicus. The molecular modelling and bioinformatics liability applied in this study have led to the realisation of a number of profound milestones, among them the cross-species network investigation among *Clavibacter michiganensis* subsp. Sepedonicus with Solanum tuberosum, conducted on STRING and CytoHubba. The results indicated that the "pyrC" gene influenced the potatoes. The protein sequence of the "pyrC" gene was retrieved through Cytoscape, and then the SWISS-MODEL tool was used to generate the three-dimensional protein structures for further docking studies. Literature review, data extraction in PubChem led to the creation of a library with 29 antimicrobial phytochemicals. The phytochemical screening with ADMETLab 3.0 and Lipinski's rule of five gave 28 compounds with favourable pharmacokinetic and pharmacodynamic features. In SeamDock molecular docking analyses, the "Berberine" compound has the most negative binding energy of -7.15 and the best binding affinity with the "pyrC" protein. Hence, it is supposed to have strong antibacterial activity against the subspecies of *Clavibacter michiganensis* Sepedonicus. This molecule also exhibited the strongest antagonistic action against *Clavibacter michiganensis* subsp. Sepedonicus, these results demonstrate the potential of Berberine as a biopesticide and note the complementary roles of bioinformatics, virtual screening, and molecular modelling for developing plant-based antiviral medication. The findings potentially open further experimental validation and possible berberine development as a long-term measure toward better yield and health of potato crops.

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