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Research Article

Evaluation of phenolic and antioxidant profiles of pink Guava peel (*Psidium guajava* L. cv Arka kiran) during fruit ripening and its *in silico* Anti SARS-CoV-2 property

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Abstract
Guava (*Psidium guajava* L.) is a highly nutritious and economically important fruit. Although fruit peel is generally regarded as a waste, researchers believe that the peel of the guava is rich in bioactive constituents, even higher than the fruit's flesh. The present study aimed to estimate phenolic content (total phenolic and total flavonoid) and assess antioxidant properties of guava fruit peel (pink variety, cv Arka kiran) by 2,2-di (4-tert-octylphenyl)-1-picryl-hydrazyl (DPPH), 2,2′-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid (ABTS) and Ferric Reducing Antioxidant Potential (FRAP) assays at five different ripening stages (stage 1 to 5). The TPC and TFC assays were performed by Folin-Ciocalteu and aluminium chloride ($AlCl_3$) methods, respectively. The molecular docking experiment between the major phenolic of guava peel, Catechin and the spike protein of SARS-CoV-2 was performed by the Dockthor online server. Results showed that the peel had high phenolic (highest TPC and TFC, 7307.3 mg gallic acid equivalent/g dry weight [DW] and 433.9 mg quercetin equivalent/g DW, respectively) and antioxidant values (highest DPPH, ABTS and FRAP values 4784.8, 206.6 and 2451 mg ascorbic acid equivalent/g DW, respectively) throughout all stages, although there was a gradual decline in the activity at the later stages. Furthermore, it was found that catechin had a strong binding affinity (-7.591 kcal mol^{-1}) with the spike protein, *in silico* when compared with the control drug ceftazidime (-7.250 kcal mol^{-1}). The overall outcome of our experiemnts revealed that guava peel could be explored for future pharmacological applications through *in vivo* studies, and the ‘green mixed with the yellow’ stage of ripening is optimum for such studies.

Keywords: Antiviral, COVID 19, Bioactivity, Fruit skin, Phenolics

INTRODUCTION

Fruits are major horticulture products (Kumar *et al*., 2020) and peel is the outermost protective part of covering the pulp of fruits and is known by various names such as husk, skin, or rind. It is generally considered inedible and recognized as solid waste (Pathak *et al*., 2017). Literature showed that approximately 25 to 30% of total fruit production is wasted as peel (Bhardwaj *et al.,* 2022). However, fruit peel is rich in fibres, vitamins, minerals, and antioxidant molecules (Ayala-Zavala *et al*., 2010; Bhardwaj *et al*., 2022). It has been reported that the antioxidant content of the peel is 328 times higher than that of the fruit pulp, in general (https://exclusives.ca.uky.edu/2021/fcs/fruit-and-vegetable-peels-contain-many-nutrients). Therefore, fruit peel can be considered as a potential source of nutrition.

India is considered as the top producer of fruits and guava (*Psidium guajava* L.) fruit constitutes major part of it (Bogha *et al*., 2020; Sharanaiahswamy *et al.,* 2022). Guava fruit is rich in phytochemicals and found to be effective in treating multiple aliments such as inflammation (El-Ahmady *et al*., 2013), diabetes (Yen *et al*., 1992), microbial infection (Oboh *et al.,* 2015) and even cancer (Polinati *et al*., 2022). Although several scientific works have been done on the fruit, studies are limited to the peel. Among these limited studies, Bashir and Abu-Goukh (2003) reported that guava peel contains higher polyphenolic compounds than pulp. Recently, Suwanwong and Boonpangrak (2021) also reported similar observations for Thailand cultivars (Kimju, Paen Sitong, and Paen Saidang). Guava peel is abundant in chlorophyll (green) and carotenoid (yellow) pigments (Corrêa *et al.,* 2011), and these pigments are highly correlated with powerful antioxidant capacities (Lu *et al*., 2021). It is a climacteric fruit and along with the pulp, its peel also shows substantial change in the phenolic constituents (De Pradhan and De, 2020) and antioxidant properties during the ripening progression. In the case of the guava peel, literature is scarce on such alternations.

The viral disease COVID-19 caused by the pathogen SARS-CoV-2 claimed 6,954,336 lives so far across the globe as per the recent estimate by WHO (https://www.who.int/emergencies/diseases). Although, vaccines are successfully deployed to curtail the spread of the disease, however, various studies equally proved the efficiency of phytochemicals to treat multiple diseases including diabetes, cancer and COVID 19 (Ferdinand and Hartanti, 2023; Parihar *et al*., 2023; Ferdinand *et al.,* 2023). Molecular docking is considered as an advanced tool for screening drug-like compounds since this technique is fast and non-expensive. In the backdrop, the present study aimed to evaluate phenolic constituents (total phenolic and flavonoid content) and antioxidant activities of the peel of g the red guava (cv Arka kiran) during five ripening stages and, finally, targeting the SARS-CoV-2 spike protein by the major guava peel phytochemical catechin, through *in silico* molecular docking study.

MATERIALS AND METHODS

Plant materials and reagents

Dark green and immature (stage 1) pink guava fruits (*Psidium guajava* L. cv Arka kiran) were collected from the Indian Institute of Horticultural Research (IIHR), Hessaraghatta, Bangalore. The fruits were kept at room temperature (28±2°C) until they became completely yellow with dry peel (stage 5). Sampling was done for all five stages (stage 2: light green; stage 3: green mixed with yellow; and stage 4: complete yellow) in a specific time interval. DPPH (2,2-di (4-tert-octylphenyl)-1-picryl-hydrazyl), ABTS (2,2′-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) and reference standards were obtained for Sigma Aldrich INC, USA. All other reagents used here were of analytical grades and obtained from Sisco Research Ltd. (SRL), India.

Extraction

Fruit peels were collected from each stage and oven-dried in a hot air oven at 40°C. Afterwards, the respective dried fruit peels were ground to powder using a mixer and stored in an air-tight container at 4°C until further use. Later, the respective peel samples (as stored stage-wise) were extracted by using hydro-methanolic (85%) solution for three days at 37°C temperature. Finally, air-dried extracts were stored in the cold room (4°C) and subjected to further experimentations as per the requirement.

Quantitative estimation of phenols of peels

Determination of total phenolic content (TPC)

The total phenolic content of the peel extracts of different stages was estimated by the method described by Bylappa and Nag, 2023; Nag *et al*. (2013). Briefly, 0.5 ml of guava fruit peel extract, 5 ml of FC reagent (1:9 dilution with double distilled water), and 4 ml of aqueous sodium carbonate (1M Na_2CO_3) solution were incubated together for 15 min. The reading was taken Spectrophotometrically (Shimadzu, UV 1900) at 700 nm and the result was expressed in mg gallic acid equivalent (GAE) /100 g of Dry weight (DW) using a gallic acid standard curve:

$$y = 0.0011x + 0.0065,\ R^2 = 0.9921\ (0\text{-}500\ \mu g/ml) \qquad \text{Eq. 1}$$

All the experiments were done in triplicates.

Determination of total flavonoid content (TFC)

The total flavonoid content of the peel extracts of different stages was estimated by the method as described by (Bylappa and Nag, 2023; Nag *et al.,* 2013). Briefly, 0.5 ml of guava fruit peel extract and aqueous aluminium chloride solution (2%) were incubated together for 15 min. The reading was taken spectrophotometrically (Shimadzu, UV 1900) at 420 nm and the result was expressed in mg quercetin equivalent (QUE) /100 g of Dry weight (DW) using quercetin standard curve:

$$y = 0.0017x - 0.0164,\ R^2 = 0.9974\ (0\text{-}500\ \mu g/ml) \qquad \text{Eq. 2}$$

All the experiments were done in triplicates.

Evaluation of antioxidant properties

DPPH radical scavenging assay

The DPPH radical scavenging assay was performed as per Bylappa and Nag (2023); Nag, Banerjee, *et al*. (2021). Briefly, 10 µl of the peel extract was added to 2 ml of 6×10^{-5} M DPPH methanolic solution and incubated at dark for 30 min. The reading was taken spectrophotometrically (Shimadzu, UV 1900) at 517 nm. The result (%inhibition) was expressed in mg ascorbic acid equivalent (AAE) /100 g of Dry weight (DW) using an ascorbic acid standard curve (0-500 µg/ml, $y = 0.07x + 7.8667$; $R^2 = 0.9924$).

The percentage of inhibition (I%) of DPPH radicals by peel extract was estimated using the following formula:

$$I\% = (A_{DPPH} - A_{sample}) / A_{DPPH} * 100 \qquad \text{Eq. 3}$$

A_{DPPH}: absorbance of DPPH + solvent, A_{sample} = absorbance of DPPH + antioxidant sample in the solvent. All tests were carried out in triplicates.

ABTS radical scavenging assay

The ABTS radical scavenging assay was performed as per Bylappa and Nag (2023); Nag, Banerjee*, et al.* (2021). Briefly, $ABTS^+$ solution was prepared by incubating ABTS (7 mM) and Potassium persulfate (2.45 mM) solution mixture (1:1) for 24h at dark. Finally, the absorbance of the solution was adjusted to 0.7 ± 0.02 at 734 nm by diluting it with methanol. 200 µl of the peel extract was then added to 2 ml of $ABTS^+$ solution and incubated at dark for 2 min. The reading was taken spectrophotometrically (Shimadzu, UV 1900) at 734 nm and the result (%inhibition) was expressed in mg ascorbic acid equivalent (AAE) /100 g of Dry weight (DW) using ascorbic acid standard curve (0-40 µg/ml, y = 1.7402x - 0.8272; R^2 = 0.9958). The percentage of inhibition (I%) of DPPH radicals by peel extract was estimated using the following formula:

$$I\% = (A_{ABTS} – A_{sample}) / A_{ABTS} * 100 \qquad \text{Eq. 4}$$

A_{ABTS}: absorbance of ABTS + solvent, A_{sample} = absorbance of ABTS + antioxidant sample in the solvent. All tests were carried out in triplicates.

Ferric Reducing Antioxidant Potential (FRAP) assay

The FRAP assay for the peel extracts of different stages was estimated by the method as per (Bylappa and Nag, 2023; Nag, Banerjee, *et al.,* 2021). Briefly, 0.1 ml of guava fruit peel extract and 3 mL of FRAP reagent (10 ml of 300 mM Na acetate buffer, pH 3.6; 1 ml of 10 mM TPTZ in 40 mM HCl; and 1 ml of 20 mM $FeCl_3$) were incubated together for 4 min. The reading was taken spectrophotometrically (Shimadzu, UV 1900) at 593 nm and the result was expressed in mg ascorbic acid equivalent (AAE) /100 g of Dry weight (DW) using ascorbic acid standard curve:

$$y = 0.0079x + 0.4039; R^2 = 0.9784 \ (5\text{-}90 \ µg/ml) \qquad \text{Eq. 5}$$

All the experiments were done in triplicates.

***In silico* molecular docking study**

Preparation of proteins

The three-dimensional protein structure of SARS-CoV-2 spike was downloaded from RCSB PDB (PDB id 6M0J, Chain E, X-Ray Diffraction, Resolution 2.45 Å) and processed as mentioned in our previous study (Nag *et al.,* 2022) by using Swiss PDB Viewer software. The protein structure was optimized through energy minimization, non-polar hydrogens removal, and polar hydrogen addition by using SwissPDB viewer and Maestro 13.3 software.

Preparation of ligand

Guava peel is a rich source of catechin. Marina and Noriham (2014) quantified 1523.79 mg catechin from 1 g of the guava crude peel extract. Catechin and its derivatives also were commonly reported from different parts of guava, including peel (Liu *et al*., 2018). Considering the evidence, we selected the compound catechin for our *in silico* study. Three-dimensional structures of the phytochemical catechin and the control drug ceftazidime were downloaded from the PubChem (https://pubchem.ncbi.nlm.nih.gov/) database. Ceftazidime was selected as the control based on its inhibition potential against the SARS-CoV-2 Spike protein- human ACE2 complex (Lin *et al*., 2021). Avogadro software was used for the optimization of the ligands. Energy minimization of the compounds was performed by applying the universal force field (UFF) algorithm. Further polar hydrogens were added to the structures at the physiological pH 7.4 (Cho *et al*., 2022; Hanwell *et al.,* 2012).

Molecular docking

Molecular docking with catechin and the SARS-CoV-2 Spike protein was performed by the DockThor web server (https://dockthor.lncc.br/v2/). Dockthor houses the Santos Dumont supercomputer and the docking tools MMFF Ligand and PdbThorBox (Santos *et al*., 2020). The molecular docking results were presented as the binding energy (kcal mol^{-1}) and compared with the control drug ceftazidime. Discovery Studio 2021 (BIOVIA, San Diego, USA) was used to evaluate the interaction between residual amino acids and ligand atoms. The Spike protein and hACE2 interaction site were targeted as the target binding pocket, and the grid was set up as center x/y/z = − 39/36/8 and size x = 24/29/20 as per our previous study (Nag, Paul, *et al.,* 2021).

Statistical analysis

A one-way ANOVA with Tukey post-doc test was performed to statistically compare phytochemical (TPC-TFC) and antioxidant (DPPH, ABTS and FRAP) data using Minitab 18 statistical software. Statistical significance was set as $p \leq 0.05$.

RESULTS AND DISCUSSION

Estimation of phenolic constituents (TPC and TFC)

The present study observed the highest amount of phenolic content (7307.2 mg GAE/100 g DW) in the stage 3 ripening stage of the Guava Arka kiran (AK)peel. A similar observation was recorded for the total flavonoid content (433.9 mgGAE/100 g DW) (Fig. 1). In agreement with present findings, earlier researchers showed that guava peel is rich in phenolics and flavonoids. Liu *et al.* (2018) reported high TPC and TFC in the guava peel (39.65 mg GAE/g DW) and TFC (19.72 mg Rutin/g DW) compared with the flesh part. Jiménez -Escrig *et al*. (2001) were able to extract approximately double the amount of extractable phenol in the guava peel (58.7 mg GAE/kg dry matter) than the flesh part (26.3 mg GAE/kg dry matter). Further, a steady increase in the phenolic content of AK peel as the fruit

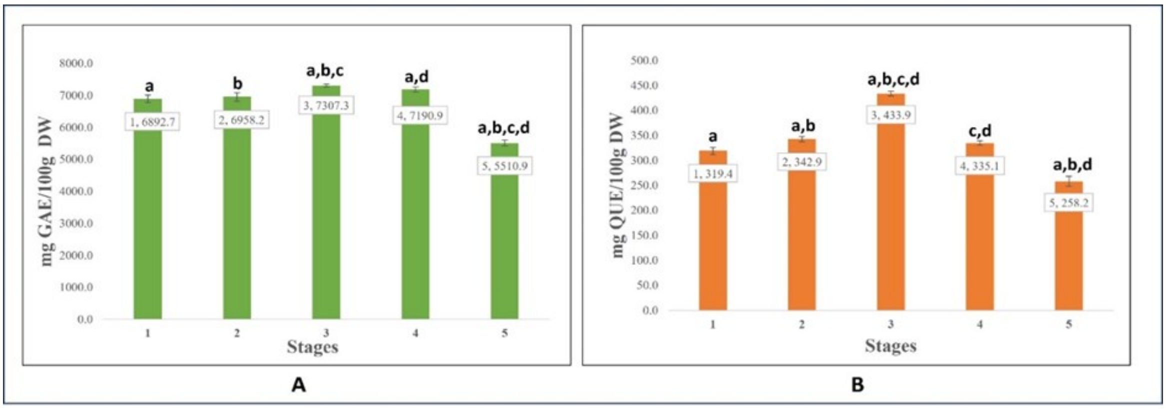

Fig. 1. *Estimation of Total Phenolic Content (A) and Total Flavonoid Content (B) at different ripening stages (1to 5) of hydro-methanolic extract (85%) of Arka kiran; GAE: Gallic acid equivalent, QUE: Quercetin equivalent; same letter represents statistically significant difference (p≤ 0.05) in One way ANOVA (Tukey post-hoc test)*

progressed from maturation stage one to three (6892.7 to 7307.3 mg GAE/100 g DW) and gradually decreased at stage four and five (7190.9 and 5510.9 mg GAE/100 g DW). For TFC, the present study also observed a similar trend (319.4 to 258.2 mg QUE/100 g DW). In agreement with the present study, a decrease in the phenolic and flavonoid content in the peel during guava fruit ripening has been reported elsewhere (De Pradhan and De, 2020). Bashir and Abu-Goukh (2003) showed that phenolic content in the white and pink-fleshed guava peels decreased significantly to ~350 to 75 and ~60 to 25 mg/100 g fresh weight, respectively.

Evaluation of antioxidant properties

In the present study, the peel of AK was found to be rich in antioxidant properties. The peel extract showed high antioxidant values in all three assays (DPPH, ABTS, and FRAP). While both radical scavenging assays like DPPH and ABTS showed the highest antioxidant potentials (4784.80 and 206.6 mgAAE/100 g DW, respectively) at stage 1 and 3, respectively, the highest FRAP value was recorded in the stage I (2451.0 mgAAE/100 g DW) (Fig. 2). Similar to TPC and TFC, the study observed the decline of antioxidant capacities for all three assays. Although limited studies are performed, nevertheless high antioxidant capacities of the guava peel extract are reported consistently. When compared with flesh and peel, Chen *et al*. (2015) reported that FRAP antioxidant value in guava peel (57.73 µmol Fe (II)/g) was much higher than the flesh (13.73 µmol Fe (II)/g) and seeds (16.53 µmol Fe (II)/g). In a similar experiment, Liu et al. (2018) compared antioxidant levels in guava's seed, peel and flesh. They showed that the DPPH assay in the peel (264.30±5.39 µmol TE/g DW) revealed three- and four-fold antioxidant capacities than flesh (98.78±3.40 µmol TE/g DW) and seed (62.84±2.81 µmol TE/g DW) extracts, respectively. Similar observation was documented for ABTS and FRAP assays by the authors, as well. Antioxidants mitigate the oxidative damage induced by reactive oxygen species, preventing the body from deleterious health conditions (Kasote *et al*., 2015). Considering this, guava peel rich in antioxidants, could be utilized as a therapeutic supplement for neutralizing reactive oxygen species.

Molecular Docking and Interaction Analysis

Catechin had higher binding potential (-7.591 kcal mol^{-1}) with the SARS-CoV-2 spike protein than the control drug ceftazidime (-7.250 kcal mol^{-1}) (Fig. 3). The amino acid interaction of catechin-protein and ceftazidime-protein are showed in Table 1. In agree-

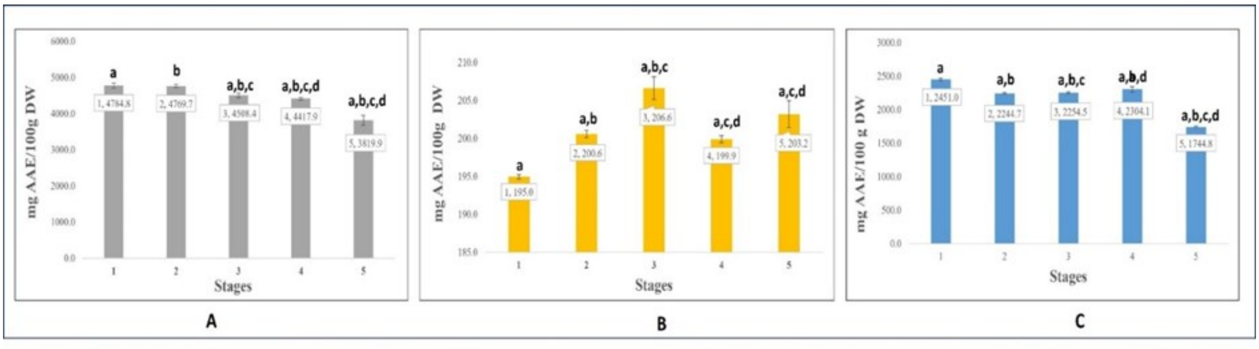

Fig. 2. *Evaluation of DPPH (A) and ABTS (B) and FRAP (C) antioxidant properties at different ripening stages (1 to 5) of hydro-methanolic extract (85%) of guava (Arka kiran); AAE: Ascorbic acid equivalent, same letter represents statistically significant difference (p≤ 0.05) in One way ANOVA (Tukey post-hoc test)*

Table 1. Residual interaction between target protein and ligands (Catechin and Ceftazidime)

Interaction types	Ceftazidime	Catechin
Conventional H bond	TYR117E, GLN161E	ARG71E, GLU74E, ASN116E
Carbon Hydrogen bond	-	-
Pi-Alkyl		ARG71E
Pi-Cation	-	-
Pi-Pi T shape bond	TYR117E	-
Attractive charge	-	-

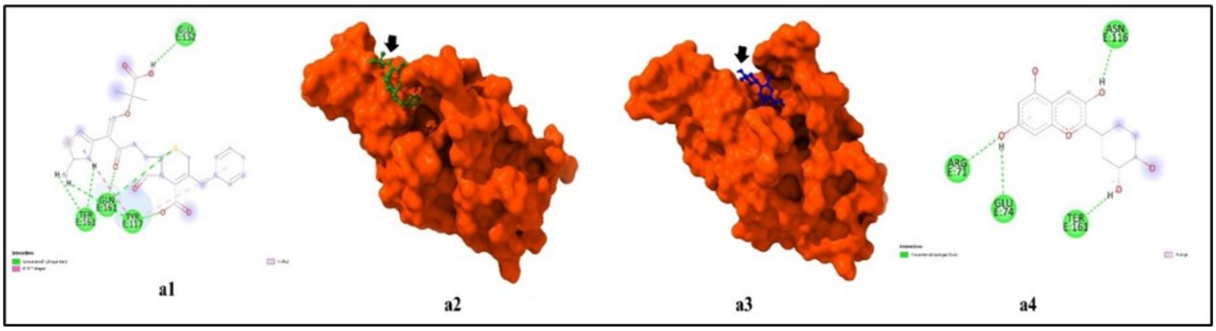

Fig. 3. *Interaction of SARS-CoV-2 Spike protein and ligands (a1 and a2: 2D and 3D interaction of control drug ceftazidime and protein respectively; and a3 and a4: 2D and 3D interaction of catechin and protein respectively); Arrow indicates the ligands*

ment with the present result, literature show that catechin had higher inhibitory potential towards the spike protein of SARS-CoV-2. Jena *et al.* (2021) reported that catechin has a higher binding affinity towards the S protein with a binding affinity -10.5 kcal mol^{-1}. Catechin derivatives were also found to target other proteins of SARS-CoV-2, namely, main protease (M^{pro}) and 3C-like protease (Shaik *et al*., 2022).

Conclusion

The peel extracts of guava (Arka kiran) showed a gradual decline of phenolic content and antioxidant values as it proceeded from the early stage (stage 1) to the fully ripe stage (stage 5). In general, guava peel extract was found to be rich in phenolics and antioxidants. Finally, Catechin, a major bioactive molecule from the guava peel, was found to inhibit SARS-CoV-2 *in silico* by binding to the spike protein.

Conflict of interest

The authors declare that they have no conflict of interest.

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