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Influence of Propylene Glycol Concentrations in Mangostin Pericarp Extract Gels Formulation: Gels Physical Characteristics, Antibacterial Activity Against *Staphylococcus aureus*, and Functional Antioxidant Activity Based on Radical 2,2-diphenyl-1-picrylhydrazyl Scavenging Activity

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ABSTRACT

Mangostin (*Garcinia mangostana* L.) fruit pericarp (GMP) extract has been shown to have antimicrobial and antioxidant activities. This study aimed to formulate and evaluate gel formulations of GMP extract using sodium carboxymethylcellulose as a gelling agent and propylene glycol (PG) in varying concentrations (i.e. 0-40%). GMP extract was evaluated for total mangostin content and antioxidant activity based on 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging method. Physical gel characteristics were also examined. All gels had similar pH and spreadability, however, gel with 40% PG produced significantly lower viscosity. Antibacterial activities against *S.aureus* were shown to be the same among GMP extract gels. The antioxidant activity of all GMP extract gels could be confirmed based on the radical DPPH scavenging method. PG content of 40% significantly reduced the increase of GMP extract gel viscosity after being stored for four weeks at room temperature. Additionally, the lowest syneresis was also shown for GMP extract gel with 40% PG content.

Keywords: Mangostin fruit pericarp extract; gel; propylene glycol; antibacterial; antioxidant

INTRODUCTION

Topical products that promote healthy skin have been explored and developed continuously. As the outer part of the human body, skin continuously exposes to exogenous stimuli such as bacterial pathogens as well as ultraviolet light. Botanical extract rich in polyphenols content offers a great material source for topical application. Studies documented that polyphenols have remarkable antimicrobial and antioxidant activities. High polyphenols content can be found, for example, in some of the fruit peel such as pericarp of mangostin (*Garcinia mangostana* L.) fruit. It has been used traditionally mostly in the Southeast Asia region for skin infection and wound therapy (Obolskiy *et al.*, 2009). The pericarp of mangostin fruit has a high content of xanthones, a class of polyphenolic compound, which posses many pharmacological activities including antimicrobial and antioxidant (Obolskiy *et al.*, 2009, Suttirak and Manurakchinakorn, 2014)

A gel is a popular semisolid product in topical pharmaceutical as well as cosmetic products. It offers several benefits such as less greasy, good emolliency, easily spreadable, and easily removed. In gel formulation development, designing formulation composition is a crucial process. The study shows the significance of vehicle composition on the efficacy and acceptability of topically applied products (Shukr and Metwally, 2013).

Being one of the key components in a gel formulation, the gelling agent has been shown to determine gel appearance, viscosity, pH, and spreadability. Furthermore, the extent and rate of drug release from gel formulations were also influenced (Helal *et al.*, 2012). Sodium carboxymethylcellulose (Na CMC) is a cellulose derived gelling agent used in topical gel formulations (Maswadeh *et al.*, 2006, Ghorpade *et al.*, 2012). Shukr and Metwally (2013) used Na CMC, carbopol 940, and hydroxypropylmethylcellulose as gelling agents to formulate lemongrass oil gel for antibacterial activity. Na CMC-based gel was shown to have superior spreadability among other gels, however, its antibacterial activity was lower than that of carbopol 940–based gel.

PG is a widely used excipient in a gel formulation. It is usually included in gel formulation as a humectant, co-solvent, and/or penetration enhancer (Shukr and Metwally, 2013). While its inclusion in formulation could aid in chemical solubilization, to some degree, PG could affect drug release (Güngör and Bergişadi, 2004).

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Table I. GMP extract gel composition

Formulation	Gel Compositions (%)			
	F1	F2	F3	F4
Mangostin fruit pericarp extract	20	20	20	20
Sodium carboxymethylcellulose	2	2	2	2
Propylene glycol	0	10	20	40
Methylparaben	0.10	0.10	0.10	0.10
Water	77.9	67.9	57.9	37.9

Lower antibacterial activity of Na CMC-based gel containing PG has been reported (Shukr and Metwally, 2013). PG concentration in topical gel needs to be carefully chosen.

This research aimed to formulate GMP extract gel using Na CMC as the gelling agent and to evaluate the influence of gel composition varying in PG concentrations. Physical gel characteristics i.e. visual homogeneity, pH, viscosity, spreadability, and syneresis were examined. The influence of PG content in GMP extract gels on their antimicrobial activity was investigated using *Staphylococcus aureus* as the microbial model. Additionally, since GMP extract has been reported to have antioxidant activity, the functional antioxidant activity of GMP extract and the gels were also tested based on DPPH radical scavenging activity method. Changes in gel physical characteristics were followed after 4 weeks of storage at room temperature.

METHODOLOGY

Materials

Dried Garcinia Mangostana Pericarp (GMP) extract was extracted using 70% ethanol (batch number 111PP01.2 purchased from PT. Borobudur Plant). The α-mangostin (analytical grade, purity of 96%) and 2,2-diphenyl-1-picrylhydrazyl radical (DPPH) were bought from Sigma Aldrich. Ethanol and methanol were analytical grade & purchased from E Merck. *Sodium Carboxymethylcellulose* (Na CMC), propylene glycol (PG), methylparaben, were pharmaceutical grade and purchased from the local store (local supplier).

Methods

Quantification total mangostin in GMP extract

Mangostin in GMP extract was quantified based on the UV spectrophotometry method (Pothitirat and Gritsanapan, 2008, Aisha *et al.*, 2013). Briefly, the calibration curve was made using α-mangostin as a reference. α-mangostin was weighed and diluted with methanol to make a concentration of 200 μg/mL. From this stock solution, a range of α-mangostin concentrations of 0,20-12,00 μg/mL was made. The absorbance of each concentration was made at a maximum wavelength (320 nm). GMP extract was weighed (200 mg), added with PG in a volumetric flask to make a volume of 10 mL and sonicated (15 min). The sample was taken, diluted 250-times with methanol, and the absorbance was measured at the maximum wavelength (Kuswahyuning *et al.*, 2019).

GMP extract gel formulations

GMP extract gels composition is presented in Table I. Dry GMP extract was added with water (F1) or PG (F2, F3, and F4) then mixed and sonicated. Na CMC, which had been hydrated overnight, stirred and added with methylparaben and water. GMP extract dispersion was slowly added to the gel base with continuous stirring (750 rpm, 10 min). Four GMP extract formulations with composition similar to Table I but without a gelling agent (Na CMC) were also made for antibacterial test purpose, namely FWG1 FWG2, FGW3, and FWG 4.

Antioxidant activity based on radical DPPH scavenging method

GMP extract antioxidant activity was evaluated based on a previously published study (Kuswahyuning *et al.*, 2019). Briefly, GMP extract was prepared at concentrations of 2-27 μg/ml. Sample (0.1 ml) was added with ethanol (1 ml), acetate buffer pH 5.5 (1 ml), and ethanolic DPPH solution (0.4 mM 0.5 ml). The reaction mixture was measured after 30 min at the maximum wavelength (522 nm). The result was expressed as concentration GMP extract that result in 50% radical DPPH scavenging activity (IC_{50}).

GMP extract gels were also assessed using radical DPPH scavenging activity. The gel was weighed (100 mg) and added with 20% ethanol to make a volume of 10 ml. Following appropriate dilution (5-times), sample (0.1 ml) was tested for DPPH scavenging activity as described above. The final concentration of GMP extract in the reaction medium was $9.6.10^{-3}$ mg/ml. GMP extract as raw

material was also tested as the method above. Additionally, the GMP extract-free formulation was also tested.

***In vitro* antibacterial activity**

Staphylococcus aureus was incubated in a sterile Nutrient Broth (NB) at 37°C for 24 h. *S. aureus* was diluted with NB to make a concentration of 1 x 10^7 CFU/ml. One hundred microliters of 1 x 10^7 CFU/ml of bacterial inoculum was poured on a plate and added with Nutrient Agar (NA) (10 ml) to make *S. aureus* suspension of 1 x 10^5 CFU/ml. Wells (5 mm) were put in the NA. Forty microliters of formulations were loaded into the wells then incubated at 37°C for 24 h. The diameters of the clear zone that indicated the inhibition zones were measured. GMP extract gel base (without GMP extract) was also tested. 1% of chloramphenicol was used as a reference. Results were the average of three replicates.

GMP extract physical gel evaluations

Visual homogeneity

Gel visual homogeneity was evaluated based on visual inspection after the gels have been set in the container. The presence and appearance of any aggregates were inspected.

pH evaluation

The gel was weighed (1 g) and added with water to make a volume of 10 ml. pH was measured using a calibrated pH meter. Results were the average of three replicates.

Viscosity

Viscosity was measured using a viscometer (*Brookfield* DV-1 *prime*) with a spindle no. 6 at 100 rpm. Results were the average of three replicates.

Syneresis

Gel (10 g) was put into a pre-weighed glass container and sealed with a plastic wrap film. The glass containers containing gel were stored at 10^0C for predetermined periods i.e. 24, 48, 72 h. Each period, the container was taken and water condensed on the glass container was removed with tissue paper then weighed with an analytical balance. All measurements were conducted in triplicates. Syneresis (%) was calculated as the weight difference between initial gel weight and weight after treatment (Kuncari *et al.*, 2014). Results were the average of three replicates.

Spreadability

The spreadability of the gel was evaluated by weighing the gel (0.5 g) and placed in the middle of the scaled round glass plate. Another glass plate was put on top of the gel and given a total load of 150 g for a predetermined time (total of 7 min). Spreadability was measured as the length of the diameter of the spread gel (Helal *et al.*, 2012). Results were the average of three replicates.

Physical stability of GMP extract gels

GMP extract gel formulations were kept in a sealed plastic container and stored at room temperature (28 ± 2°C) for 28 days. During predetermined time i.e. 1, 3, 5, 7, 21, and 28 days, formulations were evaluated for physical stability i.e. pH, spreadability, and viscosity.

Data/Statistical analysis

All of the data was expressed as mean ± SD (standard deviation). One-way ANOVA followed by the Tukey test was performed for the statistic analysis. A significance level was set at $p < 0.05$.

RESULT AND DISCUSSION

Mangostin fruit pericarp contains xanthones such as α-mangostin, β-mangostin, and γ-mangostin. The major constituent in mangostin peel was identified as α-mangostin, which was reported to have antimicrobial and antioxidant activities. Quantification total mangostin from GMP extract and GMP dry powder has been successfully done based on the UV-spectrophotometric method (Pothitirat and Gritsanapan, 2008, Aisha *et al.*, 2013) and High-Performance Liquid Chromatography (Pothitirat and Gritsanapan, 2009). The UV-spectrophotometric method was suggested as a quick and simple method to quantify total mangostin from GMP pericarp extract. Using the UV-spectrophotometric method, the present result showed total mangostin in dried GMP extract was 21,16 ± 0,01%. Other studies reported content total mangostin from GMP extract of 35.68 - 36.92% (Pothitirat and Gritsanapan, 2008). The difference in the extract production method (e.g. extracting solvent) as well as the source of the material (e.g. place of growth, maturity stage, harvesting period) could be the reason for total mangostin content discrepancy.

Mangostin in GMP extract has been shown to have antibacterial (Obolskiy *et al.*, 2009) as well as antioxidant activities (Tjahjani *et al.*, 2014, Suttirak and Manurakchinakorn, 2014). In terms of antibacterial activity, a study by Sukatta *et al.* (2008) reported that GMP extract gel was tested against pathogens such as *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Propionibacterium acnes*. It was shown that GMP extract gel was able to inhibit the growth of all of those pathogens tested but more effective in inhibiting S.aureus growth. The present study confirmed that GMP

Table II. GMP extract gels characteristics

Formulation	Visual appearance/ homogeneity	Viscosity (mPas)	pH	Spreadability (cm)
F1	Homogeneous	3343,33 ± 100,17	5,25 ± 0,19	6.42 ± 0.33
F2	Homogeneous	3226,67 ± 109,70	5,30 ± 0,26	6.22 ± 0.88
F3	Homogeneous	3636,67 ± 232,45	5,2 ± 0,06	6.03 ± 0.25
F4	Homogeneous	2803,33 ± 89,63	5,07 ± 0,02	6.82 ± 0.28

extract showed S.aureus antibacterial activity with an average inhibition diameter zone of 14 ± 1 mm. A major constituent in GMP extract, i.e. α-mangostin, has also been reported to inhibit *S.aureus* (Al-Massarani *et al.*, 2013).

Evaluation of antioxidant activity from botanical extract can be evaluated based on several methods including DPPH radical scavenging activity. It is based on antioxidant activity to donate a hydrogen atom to capture radical DPPH (Suttirak and Manurakchinakorn, 2014). Sukatta *et al.* (2013) reported that radical DPPH antioxidative activity of the pericarp of mangosteen fruit was related to α-mangostin and γ-mangostin. Dried GMP extract used in this study was extracted using 70% ethanol and showed IC_{50} (concentration which shows 50% radical DPPH scavenging activity) of 14.94 **±** 0.26 µg/mL. This IC_{50} value was lower than that of reported by Tjahjani *et al.* (2014) who reported an IC_{50} of 6.56 **±** 0.31 µg/mL of GMP ethanolic extract, possibly because of the difference in extract material source and or harvesting time.

To develop topical GMP extract gel formulations, vehicle composition needs to be carefully considered. Some studies reported the use of Na CMC as a gelling agent with a concentration of 0.5-2% (Verma *et al.*, 2013) and 2-3% (Shukr and Metwally, 2013). It is of interest to note that those studies consisted of drugs, Na CMC, PG, and water. The discrepancy gel physical properties, as well as drug release in each of these two studies, were related to Na CMC and PG concentration.

In this study, Na CMC was used at a fixed concentration i.e. 2% since the preliminary experiment showed that at this concentration it produced GMP extract gel with desired viscosity. The study investigated GMP extract loaded gels differing in PG content i.e. 0-40% and its effects on GMP extract gel physicochemical characteristics as and antimicrobial activity. PG is one of the most popular components in topically applied product functioning for example as emollient, humectant, and co-solvent. In gel formulations studies, PG was included in formulations in varying concentrations ranging from 1-20 (Patel *et al.*, 2011, Jambaninj *et al.*, 2012, Helal *et al.*, 2012). Other studies also reported at higher PG concentrations i.e. 70% (Diez-Sales *et al.*, 2005).

Evaluation gel physicochemical properties i.e. visual inspection, viscosity, pH, and spreadability resulted in data presented in Table II. Assessment of these formulation characteristics is necessary for relation to product quality. All of the gels showed a browny color and visually homogeneous. The pH of all formulations was similar ($p>0.05$) showing average value between 5.07–5.30. A topical product is usually required to have a pH around 4.5-6.5 which is suitable for skin application (Shukr and Metwally, 2013). In terms of viscosity, the gels had an average viscosity range of 2803.33 – 3636.67 mPas. PG content of 10 and 20% did not significantly cause changes in the viscosity ($p>0.05$) compared with gel without PG. However, a significantly reduced viscosity was observed with 40% PG content ($p<0.05$). This result is in agreement with Arellano *et al.* (1999) who found that PG concentration in the gel up to 30% did not result in significant changes in viscosity. Gel viscosity was decreased when PG concentration in the gel higher than 30%. Although PG concentration influenced gel's viscosity, the spreadabilities of GMP extract gels were not statistically different among formulations ($p>0.05$) showing an average spreadability value of 6.03-6.82 cm. This spreadability is higher than that of reported for fluconazole gel i.e. 3-5 cm (Helal *et al.*, 2012). Figure 1 presents the syneresis of the GMP extract gels. All of the formulations showed higher weight loss after 72 h. The average weight loss of F1, F2, F3, and F4 were 3.37, 1.95, 1.17, and 0.37%, respectively. Increasing PG content in the gels significantly reduced syneresis ($p<0.05$).

The antimicrobial activity of GMP extract formulations was tested against S.aureus. The result is presented in Table III. *S.aureus* is a gram-positive bacteria that causes superficial skin infection (Daum, 2007). GMP extract formulations showed inhibition activity on *S. aureus*. The average diameter inhibition of F1, F2, F3, and F4 was 11.66, 13.33, 13, and 12.33 mm, respectively,

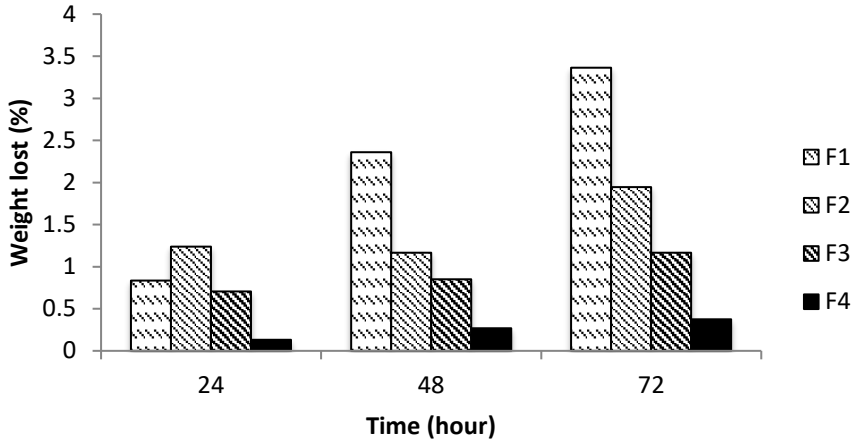


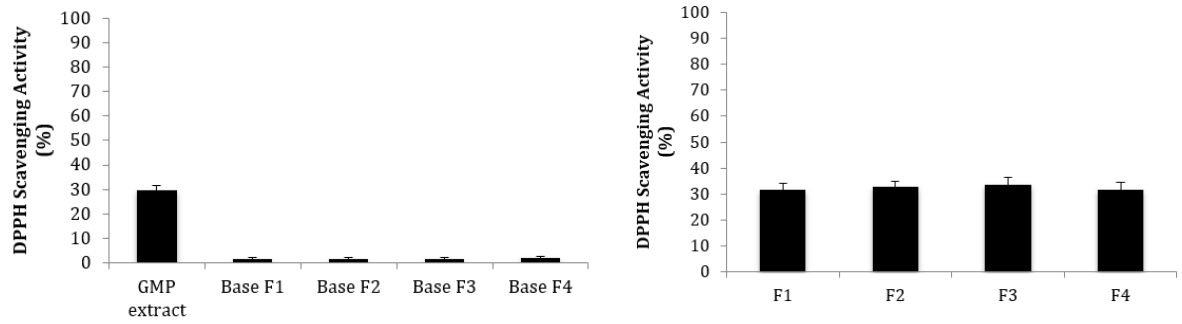
Figure 1. Syneresis of the GMP extract gels

Table III. In vitro antibacterial activity against S.aureus of GMP extract gels (F1-F4) and GMP extract formulations without CMC Na (FWG1-FWG4)

Formulation	Inhibition diameter (mm)
F1	11.66 ± 0.57
F2	13.33 ± 0.57
F3	13.00 ± 2.00
F4	12.33 ± 0.58
Gel Base	-
Chloramphenicol (1%)	38.67 ± 1.15
FWG1	14.00 ± 1.00
FWG2	13.66 ± 0.57
FWG3	13.00 ± 0.53
FWG4	14.66 ± 0.57

whereas that of the gel base did not show any inhibition. The concentration of PG content in the gels did not significantly affect the inhibitory activity against *S. aureus* ($p>0.05$). Formulations with PG addition i.e. F2, F3, and F4 produced similar S.aureus zone inhibition compared to gel without PG (F1). *In vitro* antimicrobial activity is related to the extent of drug release. The good antimicrobial activity is correlated with high drug release (Shahin *et al.*, 2011). Since GMP extract concentration in all gels was kept constant, the difference PG content in the gel was the main factor that affected the antimicrobial activity of the GMP extract gels. PG has been reported to influence drug solubility as well as vehicle viscosity. Thus difference PG content in GMP extract gels might cause changes not only in drug solubility but also in vehicle viscosity. PG influence on GMP extract solubility in the formulations is difficult to be justified as it was not measured in this study. In terms of viscosity, even though 40% PG in GMP extract gel caused significantly reduced viscosity but its antibacterial activity was similar compared with all other gels. Drug diffusivity in the formulations may be more related to the microviscosity of the vehicle rather than its macroviscosity (Diez-Sales *et al.*, 2005). Since gel viscosity might also be affected by the presence of gelling agent, to eliminate gelling agents influence, more tests on antimicrobial activity against *S.aureus* were also done using GMP extract formulations produced without gelling agent addition. The results demonstrated a relatively similar *S.aureus* inhibition zone from all formulas without a gelling agent. However, Formulation FWG1 had a significantly higher *S.aureus* inhibition zone compared to formulation F1. It suggested that the presence of gelling agent CMC-Na in F1 was responsible for the reduction of antimicrobial activity. Interestingly, FWG2, FWG3, and FWG4 demonstrated similar *S.aureus* inhibition zones. Further study is needed to evaluate GMP extract solubility as well as vehicle viscosity due to PG concentrations.

The developed GMP extract gels were also tested for their functional antioxidant activity



(A) (B)

Figure 2. The radical DPPH scavenging activity of **(A)** GMP extract and gel bases (free of GMP extract); **(B)** GMP extract gels

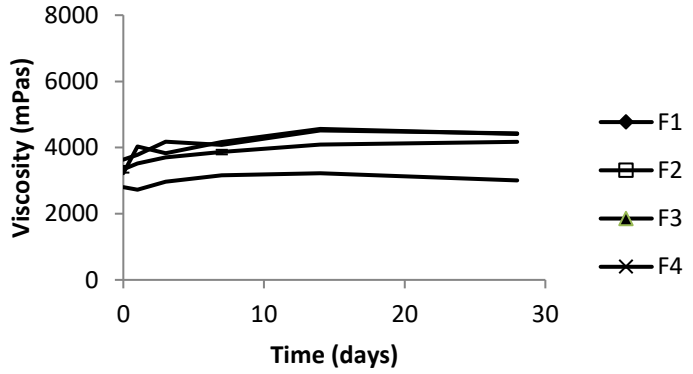


Figure 3. The viscosity of the GMP extract gels when stored at room temperature for 28 days

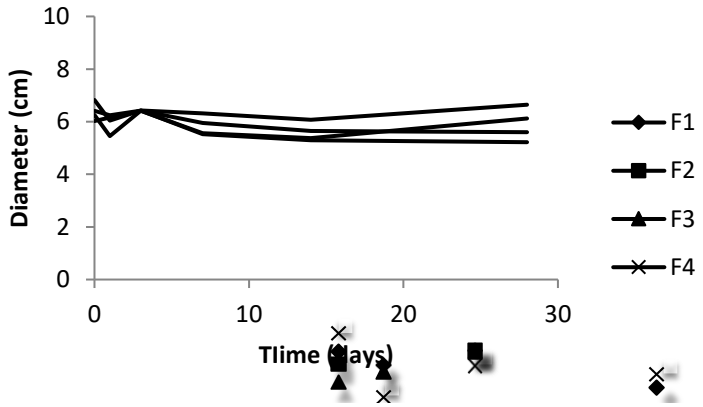


Figure 4. Spreadability of the GMP extract gels when stored at room temperature for 28 days

based on radical DPPH scavenging activity. It has been shown as a valuable tool to confirm if the formulation has antioxidant activity. Antioxidant activity evaluation based on the DPPH method has been suggested as a suitable method for formulations containing natural products which usually consists of a complex polyphenolic mixture compound (Fonseca *et al.*, 2011). The adequacy of the DPPH scavenging method to assess the functional antioxidant activity of GMP extract gel was first tested. Each of the formulations without GMP extract addition (each of gel base) showed no significant influence on DPPH scavenging activity (Figure 2). It suggested that components of gel formulations did not interfere with the DPPH scavenging assay confirming the application of the radical DPPH scavenging method for evaluating antioxidant activity in the

formulations. GMP extract demonstrated radical DPPH scavenging activity of 29.31 ± 2.31%. Compared to the same final concentration in the reaction medium, all of the formulations resulted in similar radical scavenging activity ($p>0.05$) of 31.43 – 33.25%, which suggests that antioxidant activity was maintained in all of GMP extract gels.

A preliminary stability study is usually evaluated during the early formulation development process to detect any instability that might occur. Physical gel stability was evaluated at room temperature storage for a period of 28 days. The changes in viscosity of the formulations during 28 days of storage at room temperature are shown in Figure 3. All of the formulations showed a significant increase in viscosity after being stored for 28 days ($p<0.05$) showing average viscosity value of 4173, 4406, 4426, and 3006 mPas for F1, F2, F3, and F4, respectively. There was a marked difference in the extent of the percentage increase of viscosity. Formulation F4, which had the highest content of PG, showed the lowest increase of viscosity. This result is consistent with the lowest syneresis shown from F4. In terms of pH, after 28 days of storage, F1, F2, F3, and F4 showed average pH values of 5.50, 5.02, 5.41, and 6.06, respectively. Even though there were relatively slight changes in pH values, all of the pHs of the formulations were still within a suitable pH for topical application. Spreadability values were only slightly decreased within 28 days of observation.

CONCLUSION

GMP extract gels formulated with variation in PG concentrations influenced physical gel characteristics differently. Spreadability and pH of the formulations were similar, however, viscosity was significantly decreased in GMP extract gel containing 40% PG. Interestingly, the antibacterial activity of all GMP extract gels against *S.aureus* was relatively the same. All GMP extract gels also showed antioxidant activity tested based on radical DPPH scavenging activity. Following storage at room temperature for four weeks, all GMP extract gels had unchanged spreadability and pH value but significantly changed in viscosity and syneresis. PG concentration of 40% produced significantly reduced syneresis and viscosity changes in GMP extract gel stored at room temperature for four weeks.

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