



## Formulation and Evaluation of Mangosteen (*Garcinia mangostana* L.) Fruit Pericarp Extract Gel

### *Formulasi dan Evaluasi Gel Ekstrak Kulit Buah Manggis (*Garcinia mangostana* L.)*

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### Abstract

The topical antioxidant product may be useful for the treatment of oxidative stress-related skin disorder. This research aimed to evaluate a topical gel formulation of *Garcinia mangostana* L. fruit pericarp (GMP) extract. GMP extract was formulated into a gel and characterized for its physical properties. The antioxidant activity was evaluated based on the radical 2,2-diphenyl-1-picrylhydrazyl (DPPH) scavenging activity. The ability of gel formulation to release GMP extract and promote skin delivery was estimated based on DPPH scavenging method and also compared to that of suspension form. The results showed that the GMP extract gel showed characteristics for topical application. The radical DPPH scavenging activity was confirmed both in GMP extract and GMP extract gel. *In vitro* study release showed that the GMP extract was released from gel. Some degree of GMP extract was also delivered into the shed snakeskin *in vitro*. When compared with the suspension form, GMP extract gel provided a more profoundly lower release.

### Abstrak

Produk topikal dengan aktivitas antioksidan diduga berguna untuk pengobatan gangguan kulit akibat stres oksidatif. Penelitian ini bertujuan untuk mengembangkan formulasi gel antioksidan topikal ekstrak kulit buah manggis (*Garcinia mangostana* L. (GMP)). Ekstrak GMP diformulasikan menjadi gel dan dikarakterisasi sifat fisiknya. Aktivitas antioksidan dievaluasi berdasarkan aktivitas penangkapan radikal 2,2-diphenyl-1-picrylhydrazyl (DPPH). Kemampuan formulasi gel untuk melepaskan dan menghantarkan ekstrak GMP ke dalam kulit diestimasi berdasarkan penangkapan radikal DPPH dan juga dibandingkan hasilnya dengan formulasi suspensi. Hasil penelitian menunjukkan bahwa gel memiliki karakteristik fisik untuk aplikasi topikal. Aktivitas penangkapan radikal DPPH dapat dikonfirmasi baik dalam ekstrak GMP maupun dalam gel ekstrak GMP. Studi pelepasan *in vitro* menunjukkan bahwa ekstrak GMP dapat dilepaskan dari gel. Ekstrak GMP juga dapat dihantarkan ke dalam kulit ular *in vitro*. Jika dibandingkan dengan bentuk suspensi, gel ekstrak GMP memberikan pelepasan yang jauh lebih rendah.

## INTRODUCTION

The trend in maintaining healthy skin and youthful appearance has driven the growth of topical products in the personal care industry.<sup>1</sup> Products from natural ingredients have become more popular in the market. Plant extracts, having antioxidant activity, have been explored and researched as one of the important sources of natural ingredients. They offer potential antioxidant activity, which could alleviate skin disorder and skin aging due to oxidative stress.<sup>2,3</sup> The topical application of antioxidant is considered to have beneficial effects for the skin such as in UV-induced skin damage.<sup>4-6</sup>

*Garcinia mangostana* fruit pericarp (GMP) extract has remarkable antioxidant properties.<sup>7</sup> The antioxidant activity of the GMP extract has been shown, at least, due to its phenolics and flavonoids content.<sup>7,8</sup> Even though topical formulation development of GMP extract seems to be attractive, the formulation needs to be considerably designed to allow skin delivery.<sup>9</sup>

Various GMP extract topical formulations have been researched and published.<sup>10-16</sup> Most of these studies reported topical formulation development and evaluation of formulation's physical stability. The skin delivery of GMP extract from the formulations was assessed based on *in vitro* skin penetration of mangostin<sup>11-14</sup>, which is the major component of GMP extract. Much less information is available on the skin delivery of GMP extract assessed based on antioxidant activity. In this research, we formulated the GMP extract into a topical gel formulation, evaluated its physical properties, *in vitro* release and *in vitro* skin delivery based on antioxidant activity. The *in vitro* release as well as *in vitro* skin delivery were performed to investigate if the GMP extract could be released from the gel and delivered into the skin estimated based on radical 2,2-diphenyl-1-picrylhydrazyl (DPPH) scavenging method. The ability of gel formulation to release GMP extract and deliver it into the skin was compared to that of suspension.

## MATERIALS AND METHODS

### Materials

Material used in this research were the extract of *Garcinia mangostana* L. fruit pericarp (extracted using 70% ethanol, local supplier), radical 2,2-diphenyl-1-picrylhydrazyl/DPPH (Sigma Aldrich), ethanol (E-Merck), methanol (E-Merck), sodium carboxymethyl cellulose (CMC-Na) (local supplier), methyl paraben (local supplier), and phosphate buffer saline (PBS) pH 7.4 (local supplier).

### *In vitro* antioxidant evaluation by radical DPPH scavenging

GMP extract antioxidant activity was measured using radical DPPH scavenging method as described in the previous study.<sup>15</sup> A series of GMP extract concentrations 0.05-0.70 mg/mL was evaluated for the DPPH scavenging activity. The reaction mixture consisted of acetate buffer pH 5.5, ethanol, 0.4 M ethanolic DPPH, and a tested sample. Each of the GMP extract concentrations was plotted against the corresponding radical DPPH scavenging activity (%). From this data, a linear calibration curve between GMP extract concentration and DPPH scavenging activity was constructed to estimate the antioxidant activity of the GMP extract, *in vitro* skin permeation, and *in vitro* release. The DPPH scavenging activities (%) from *in vitro* permeation and *in vitro* release studies were transformed into GMP extract equivalent using a calibration curve obtained from GMP extract DPPH scavenging activity and calculated in relation to permeation effective surface area ( $\mu\text{g}/\text{cm}^2$ ).<sup>17</sup>

### GMP extract gel formulation

The gel base was composed of 2% CMC-Na, 10% ethanol, 0.1% methyl paraben, and deionized water to 100%. CMC Na, which had been previously hydrated overnight in water, was agitated (750 rpm) then methyl paraben was added. Subsequently, GMP extract dispersion (20%) was added to the gel base with continuous stirring until uniformly

dispersed. The GMP extract in suspension was prepared by adding GMP extract (20%) in water.

#### **Antioxidant evaluation of GMP extract gel**

GMP extract gel (100 mg) was dissolved in 10 mL ethanol-PBS mixture (1:4) with the aid of sonication, and further diluted 1:4. Samples were taken (0.1 mL) and evaluated for DPPH scavenging activity based on the previously described method. The final concentration of GMP extract in the reaction medium was  $9.6 \times 10^{-3}$  mg/ml. GMP extract dispersion as raw material was evaluated at the same final concentration in the reaction medium. The GMP extract-free formulation was served as blank.

#### **Gel pH and viscosity measurement**

The gel (1 g) was diluted with water until 10 mL.<sup>18, 19</sup> The pH of the sample was measured using a calibrated pH meter. Gel viscosity (mPas) was determined using a Brookfield viscometer. The spindle (no. 6) was rotated at 100 rpm. The measurements were conducted at room temperature.

#### **Spreadability**

The gel (0.5 g) was 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 (7 min). Spreadability was measured as the length of the diameter of the spread gel.<sup>20</sup> Result was 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 gel-containing glass were stored at 10 °C for predetermined periods i.e. 24, 48, 72 h. Each time, the container was taken and water condensed on the glass container was removed with tissue paper then weighed with an analytical balance. All measurement was conducted in triplicates. Syneresis (%) was calculated as the weight difference between initial gel weight and weight after treatment.<sup>21</sup> Result was the average of three replicates.

#### ***In vitro* skin permeation**

The hydrated shed snakeskin (*Phyton morulus* sp) was placed between the donor and receptor compartment (effective surface area of 1.4 cm<sup>2</sup>). The formulation (0.8 g) was filled in the donor phase and the receptor phase (1.0 mL) was filled with 20% ethanol in phosphate buffer saline. The diffusion cell was stirred with a magnetic stirrer at 300 rpm and kept at room temperature. At the end of the permeation study (after 24 h), a sample was taken from the receptor phase (0.5 mL) and tested for DPPH scavenging activity. The shed snakeskin membrane was removed from the diffusion cell, cleaned from the formulation, and prepared for *in-vitro* skin retention studies.<sup>17</sup> Methanol (1.0 mL) was used as the solvent for skin extraction.<sup>15,17</sup> Samples (0.1 mL) were tested for DPPH scavenging activity. Four replicates were done for each of the formulations studied. The GMP extract-free formulation was served as blank.

#### ***In vitro* release**

*In vitro* release was conducted as described in the *in vitro* skin permeation but shed snakeskin was substituted with cellophane membrane. During each predetermined time, the receptor phase was sampled (0.5 mL) and the same volume of fresh receptor phase was replaced to the receptor compartment. The obtained samples were tested for antioxidant activity using the DPPH scavenging method.<sup>22</sup> The GMP extract-free formulation served as blank.

## **RESULTS AND DISCUSSION**

Studies showed that ethanolic GMP extract had radical DPPH scavenging activity.<sup>15,23</sup> Ethanolic GMP extract was often quantified in terms of  $\alpha$ -mangostin,  $\gamma$ -mangostin,<sup>8,24</sup>  $\beta$ -mangostin,<sup>24</sup> total phenol, total flavonoid, and total tannin content.<sup>25</sup> Among xanthenes derivatives in GMP extract,  $\alpha$ -mangostin was identified as the major constituent. The  $\alpha$ -mangostin,  $\gamma$ -mangostin,<sup>8,24</sup> and epicatechin were reported to have radical DPPH scavenging activity.<sup>8,26</sup> The qualitative and quantitative antioxidant

constituents of GMP extract are dependent on the type of extracting solvent.<sup>23,24,26</sup>

Our earlier studies indicated that GMP extract could be delivered into the shed snakeskin using binary solvent mixtures as the vehicles,<sup>17</sup> and some types of formulation, i.e. cream and gel.<sup>15</sup> In this present study, GMP extract was also formulated into a gel with ethanol present in the formulation.

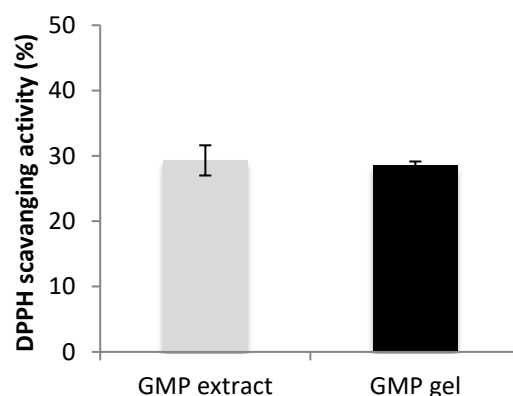
### GMP extract gel evaluation

To ensure that GMP extract gel formulation has antioxidant activity, GMP extract before and after being formulated into gel were compared for their DPPH scavenging activity as shown in Figure 1. Tested using the same final GMP extract concentration in the reaction medium ( $9.6 \times 10^{-3}$  mg/mL), GMP extract before and after being formulated into gel showed  $29.31 \pm 2.31\%$  and  $28.47 \pm 0.68\%$  DPPH scavenging activity, respectively. The result indicated that GMP extract did not lose scavenging activity when formulated into a gel ( $p > 0.05$ ). The DPPH scavenging activity of the GMP extract gel also did not change during 24 h (data are not shown), which was the necessary duration for conducting *in vitro* release and *in vitro* skin permeation studies. The gel of GMP extract was also characterized for viscosity, pH, and functional antioxidant activity evaluated based on radical DPPH scavenging activity, *in vitro* release, and *in vitro* skin penetration. Table 1 presents the gel characteristics. GMP extract-loaded gel showed a viscosity of  $3572.5 \pm 103.40$  mPas, a pH value of  $4.81 \pm 0.01$ , and syneresis of  $1.43 \pm 0.41\%$ . The gel also had a spreadability of  $3.74 \pm 0.96$  cm, which was lower compared to another study of mangosten topical gel.<sup>27</sup>

### In vitro release

The topical GMP extract skin delivery requires that extract must be able to be released from the formulation after its application. Therefore, GMP extract release from the gel was evaluated. The radical scavenging DPPH evaluation has been shown as a useful method to test the release of a topical natural product formulation having antioxidant activity.<sup>22</sup>

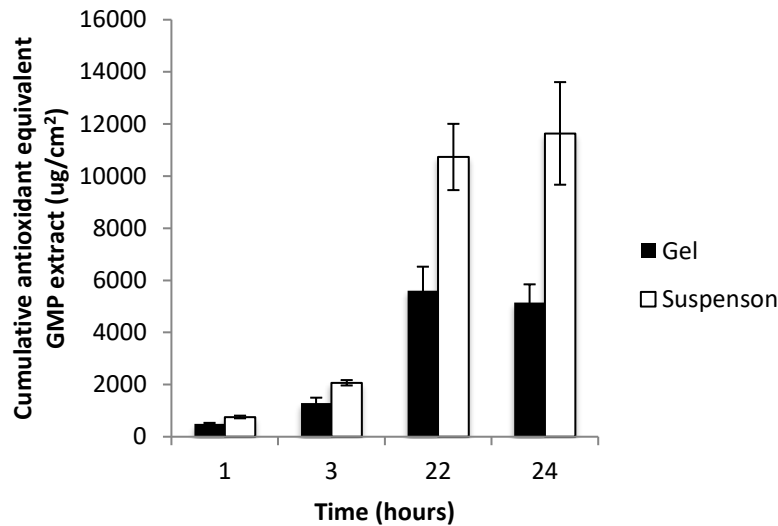
*In vitro* GMP extract release from the gel is shown in Figure 2. GMP extract, which has been released, was detected in the receptor phase using the DPPH scavenging activity method. After 24h, GMP extra



**Figure 1.** DPPH scavenging activity (%) of 10% GMP extract before and after being formulated into GMP extracts gel. The final concentration of GMP extract in the reaction mixture was  $9.6 \times 10^{-3}$  mg/mL

**Table 1.** GMP extract gel characteristic

Gel Characteristic	Average $\pm$ SD
Viscosity (mPas)	$3572.5 \pm 103.40$
pH	$4.81 \pm 0.01$
Spreadability (cm)	$3.74 \pm 0.96$
Syneresis (%)	$1.43 \pm 0.41$



**Figure 2.** *In vitro* release of radical DPPH scavenging activity equivalent GMP extract from gel and suspension as a function of time. Each point represents the mean  $\pm$  SD of four replicates.

showed a cumulative amount released of  $5145.72 \pm 701.09 \mu\text{g}/\text{cm}^2$ . It indicated that antioxidant constituents from GMP extract could be released from gel formulation. When GMP extract was formulated into suspension, the cumulative amount released was higher, i.e.  $11637 \pm 1968 \mu\text{g}/\text{cm}^2$ . The lower GMP extract released from gel could be due to the presence of ethanol in the gel formulation that acted as a co-solvent.<sup>28</sup> Moreover, the GMP extract in gel formulation exhibited a more viscous appearance than GMP extract in a suspension formulation. The high viscosity of the vehicle has been shown to reduce chemical release from the vehicle. The affinity between chemical and vehicle will also determine the *in vitro* release.<sup>29</sup>

#### ***In vitro* skin permeation**

To further evaluate if GMP extract was also able to penetrate the skin, the *in vitro* skin permeation was conducted. Additionally, GMP extract skin retention analysis was also investigated. Shed snakeskin was used as the skin membrane in this study.<sup>30</sup>

The results of *in vitro* skin permeation and skin retention study of GMP extract gel and suspension are presented in Table 2. The DPPH scavenging activity from skin retention analysis indicated that GMP extract

could penetrate and retain in the shed snakeskin. The GMP extracts from gel and suspension retained in the skin were  $42.72 \pm 3.82 \mu\text{g}/\text{cm}^2$  and  $72.41 \pm 7.66 \mu\text{g}/\text{cm}^2$ , respectively. Higher GMP extract shed snakeskin retention from GMP extract suspension than that of gel could be associated with its higher release. GMP extract skin retentions both from gel and suspension were much lower than that released from the formulations suggesting that the rate-limiting step of GMP extract skin delivery resided in the shed snakeskin penetration ability. GMP extract permeation found in the receptor phase either from gel or suspension could not be quantified since the DPPH scavenging values were under the quantification limit (6% and 9% DPPH scavenging activity in the receptor phase, respectively). The permeation result suggests that GMP extract penetration to the receptor phase was negligible. The GMP extract released from gel seems to be more retained in the shed snakeskin than permeated into the receptor phase. This result is different from *in vitro* permeation result of GMP extract gel without ethanol in the gel formulation.<sup>15</sup> In that our earlier published study, GMP extract was more penetrated in the receptor phase than retained in the snakeskin. More study needs to be done to get more understanding of GMP extract skin permeation.



**Table 2. Percentage of radical DPPH scavenging activity and corresponding GMP extract estimated to the permeation and skin retention of GMP extract formulations**

	GMP extract gel		GMP extract suspension	
	Antioxidant <sup>a</sup> (%)	Q <sub>24</sub> <sup>b</sup> GMP (µg/cm <sup>2</sup> )	Antioxidant <sup>a</sup> (%)	Q <sub>24</sub> <sup>b</sup> GMP (µg/cm <sup>2</sup> )
Permeation	7.16 ± 1.88	- *	9.48 ± 0.80	- *
Retained in the skin	18.72 ± 1.56	42.72 ± 3.82	30.85 ± 3.13	72.41 ± 7.66

<sup>a</sup>Antioxidant activity evaluated based on radical DPPH scavenging activity

<sup>b</sup> Cumulative amount of GMP extract

\* The mean value of DPPH scavenging activity is under quantification limit, so the corresponding GMP extract could not be estimated

## CONCLUSION

GMP extract could be formulated into a topical gel. The antioxidant activity was confirmed in both GMP extract and GMP extract gel. The GMP extract gel fulfilled topical gel physical characteristics. The gel of GMP extract demonstrated antioxidant release from gel formulation as detected by the DPPH scavenging method. Furthermore, GMP extract could penetrate and retain in the shed snakeskin. GMP extract gel seems to be potential to be developed and tested further as a topical antioxidant product.

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