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### Formulation and evaluation of antimicrobial herbosomal gel from Quercus infectoria extract

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Abstract. Nowadays, the use of herbal medicine is gaining importance for treating many diseases due to their significant effect and lesser side effects as compared to allopathic medicines. Phytosomal herbal formulations or herbosomes are better absorbed and produce better bioavailability than the conventional botanical extracts. Hence, this study is conducted to formulate the herbosomal gel from QI galls ethanolic extract. The QI gall was extracted using ethanol giving the percentage of yield 17%. For the High-Performance Liquid Chromatography analysis, it was revealed that the QI galls extract contains large amount of tannic acid (1794.18 mg/g) and small amount of gallic acid (76.22 mg/g). The formulation consists of 1.0% of Carbopol 940 were found to be the best formulation since it shows good physicochemical properties. pH value was 6.31 while the viscosity was 3482.3144 cps. Formulated gel showed good stability after 21 days of formulation by not showing significance changes in pH value, viscosity and spreadability. Disc diffusion method was used to determine the antimicrobial activity and the results showed the inhibition zone for P. aeruginosa was greater than S. aureus. As conclusion, the QI galls extract formulated herbosomes was showed promising results to be developed as a new antibacterial gel formulation.

#### **1. Introduction**

Herbal medicine or natural based products are gaining importance for treating many diseases due to their significant effect and lesser side effects as compared to conventional medicines [1]. The goal of topical antimicrobial therapy in skin infections is to control microbial colonization and subsequent proliferation thus promoting the healing of the wounds [1]. The emerging technology of drug delivery is being applied to phyto-pharmaceuticals to improve the bioavailability of herbal extracts for medicinal application [2]. Plant extracts can be standardized accordingly and may be formulated as phytosomes for systematic investigation for any improved potential use. Phytosomal herbal formulations are better absorbed, and as a result produce better bioavailability and actions than the conventional phytomolecules or botanical extract [2]. This formulation is also known as herbosomes. This study is conducted to formulate the herbosomal gel from *Quercus infectoria* (QI) galls ethanolic extract.

Quercus infectoria (QI) is a small tree or shrub that falls under Fagaceae (Quercaceae) family [1]. This gall is better known as manjakani among the local people in Malaysia. QI galls was originated from Western Asia and Southern Europe [1]. Galls are irregular plant growth that was produced from the chemical reaction between insects and plant hormones [1]. The QI galls is described in detail in

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ethnobotanical and literature to possess various pharmacological actions such as analgesic, antidote, anti-inflammatory, antipyretic, antiseptic, antistomatitis, deodorant, derivative, desiccant, expectorant, germicidal, hypnotic, hypoglycaemic, powerful astringent, sedative, styptic, tonic, tonic to teeth and gum, and wound healing [3]. The main component in QI galls are tannin (50-70%) and small amount of free gallic acid and ellagic acid [3]. The galls also contain gum, sugar and essential oil [3].

Lot of studies were conducted on the potential of this QI galls on their biological activity for medicinal purpose. Previous study showed that the herbosomal gel prepared using QI galls extract exhibited great physical and physicochemical properties [1]. Besides that, another study revealed that hydroalcoholic extract of QI galls can be applied to human body in more effective way when formulated in microemulsion-gel system. In this study, QI galls extract showed acceptable antimicrobial and antifungal activity against selected microbes. Optimized formulations showed acceptable pH, spread ability, in vitro diffusion and percent drug retention [4]. Furthermore, this QI galls extract also was used to prepare the formulation of in-situ herbal gel for the treatment of vagina infection. This study revealed that this QI galls extract was very effective and beneficial in the treatment of vagina infection in the form of herbal gel [5]. Therefore, the purpose of this present study was to formulate the herbosomal gel of QI galls extract and to evaluate the physicochemical properties in term of pH, viscosity homogeneity and spreadability of the herbosomal gel.

#### 2. Methodology

#### 2.1 Preparation of Quercus infectoria (QI) extract

The galls of QI were cleaned and washed with water and air dried. Then, the galls were crushed by using hammer into small pieces and ground to produce fine powder. Ethanolic extract was prepared by maceration extraction process where 100 gram of galls powder was soaked in 600 ml ethanol for 72 hours [8]. Then, the mixture was filtered using filter paper. The filtrates were subjected to rotary evaporation process to remove the ethanol. After rotary evaporation, the extract was stored at -80°C overnight. Finally, the extract was freeze dried and store at 4 °C prior used.

#### 2.2 High Performance Liquid Chromatography (HPLC)

#### 2.2.1 Quantification of gallic acid

Determination of active constituents from extracted compounds was examined using high performance liquid chromatography as described by [6] with a slight modification. In order to evaluate the quality of extracted compounds, all the samples were analysed by using High Performance Liquid Chromatography (HPLC) using gallic acid as standard. Waters 600E System Controller combined with Waters 996 Photodiode Array Detector was used and C18 column was selected as stationary phase. Meanwhile, 0.1% orthophosphoric acid (H3PO4) was consumed as solvent A and 100% acetonitrile (100%) as solvent B. Then, the flowrate of mobile phase was adjusted at 1 ml/min at 280 nm and every injection was set until achieved 10  $\mu$ L.

#### 2.2.2 Quantification of tannic acid

The concentration of tannic acid from the extracts was determined with slight modification. HPLC was performed by reversed-phase HPLC on a C18 column by using a binary gradient elution with consisting of an aqueous methanol eluent at low pH as mobile phase. The gradient system consisted of solvent A (25 ml acetic acid and 975 ml distilled water) and solvent B (99.8% methanol) pumped at 1 mL/min. The gradient started with 100% solution A and ended with 100% solution B at 30 min. The column temperature was maintained at 30°C. The sample peaks were identified by comparing with standard solution of tannic acid at 280 nm. The percentage of the tannic acid was calculated using the appropriate calibration curves [7].

#### 2.3 Formulation of herbosomal gel

Herbosomes are made by reacting the QI gall extract with soy lecithin and cholesterol in a ratio of 1:1 and dissolved them in ethyl acetate. After solubilization completed, the complex compounds formed

was removed by solvent evaporation technique [1]. Herbosomal gel was prepared by using Carbopol 940 as the gelling agent as shown in the table 1 below.

#### 2.4 Physicochemical evaluation of herbosomal gel

2.4.1 pH. The pH meter was calibrated using standard buffer solution such as pH 4.0 and 7.0. About 0.5 g gels was weighed and dissolved in 50 ml of distilled water and the pH reading were taken [1].

2.4.2 *Viscosity*. Viscosity of the formulation was determined by CCT\_8\_600110 using RST-CC Brookfield Rheometer at 100 rpm [1].

2.4.3. Spreadability. The 0.5 g gel was weighed and pressed between two horizontal plates  $(20 \times 20 \text{ cm})$ . Then 500 g weight was put on the upper plate and left for about 5 minutes. Diameters of spread circles were measured in cm. The results obtained were the average of three determinations [1].

#### 2.5 Stability Studies

The optimized formulation of herbosomal gel was selected for stability study. Two other formulations were made as control which was F5 and F6. F5 was formulated without the addition of propylparaben as stabilizer and F6 was formulated without the presence of QI galls extracts as active pharmaceutical ingredients. Stability studies was performed on these three formulations by kept them at three different temperatures, i.e.  $45 \pm 2^{\circ}$ C,  $25 \pm 2^{\circ}$ C and  $4 \pm 2^{\circ}$ C for 21 days [1]. Parameters observed for the herbosomal gel are the determination of the pH value, viscosity, homogeneity and spreadability of the herbosomal gel.

#### 2.6 Centrifugation Test

10g of herbosomal gel was added in a centrifuge tube. During centrifugation, the gel was subjected to a cycle of 3000 rpm for 30 minutes at room temperature. Centrifugation was performed by Model Eppendorf Centrifuge 5820 R [8].

#### 2.7 Agar well diffusion method

Three petri dishes were filled with nutrients agar and 80  $\mu$ l of bacteria strain in nutrients broth (S. aureus or P. aeruginosa) for each concentration range from 5.00 mg/ml to 0.10 mg/ml using half fold serial dilution. Each concentration for antimicrobial test was done in triplicate. Total concentration for antimicrobial test was 10 concentrations. The nutrient agar was air dried inside fume hood. Then, 5.0 mm<sup>3</sup> of well was bored out using pipette tip. Antimicrobial testing for herbosome gel formulation was run by impregnated 100 $\mu$ l of gel inside the well and incubated the antibacterial assay plate upright for 24 hours at 37 °C. The area of inhibition was measured using Vernier caliper for each concentration. Then, repeat the test three times for each concentration [9]. The whole step was repeated using QI galls extract. The empty well was used as control to see the natural growth of bacteria under same condition, temperature and environment.

#### 3. Results and discussion

The extraction yield of QI galls with ethanol obtained was 17%. As shown in table 1 below, the QI galls extract contains high concentration of tannic acid and small amount of gallic acid which are 1794.18 mg/g and 76.22 mg/g respectively. From the results, it was revealed that tannic acid is the major bioactive constituents in QI extract. Due to its high concentration, most of the pharmacological properties exhibited by the galls extract can be attributed to tannic acid [10].

Table 1. Concentration of gallic acid and tannic acid in Quercus infectoria (QI) galls extract.

| Sample                          | Gallic acid (mg/g) | Tannic acid (mg/g) |
|---------------------------------|--------------------|--------------------|
| Quercus infectoria (QI) extract | 76.22              | 1794.18            |

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Previous study reported lower concentration of gallic acid and tannic acid in ethanolic extract of QI galls which are 37.22 mg/g and 954.03 mg/g respectively [11]. However, this findings were also supported by previous data from past researches, which showed the presence of tannic acid, gallic acid, syringic acid, ellagic acid,  $\beta$ -sitosterol, amentoflavone hexamethyl ether, isocryptomerin, starch, essential oils, anthocyanins, methyl-betulate, methyl- oleanate, hexagalloyl-glucose and polygalloyl-glucose [12] in QI galls extract. Table 1 to 4 below showed the HPLC chromatogram for the standard and sample tannic and gallic acid in QI galls extract.

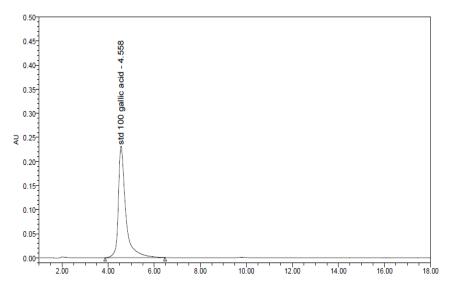


Figure 1. HPLC chromatogram of standard gallic acid

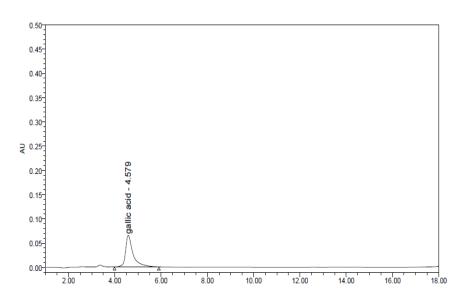


Figure 2. HPLC chromatogram for gallic acid in *Quercus infectoria* (QI) galls extract

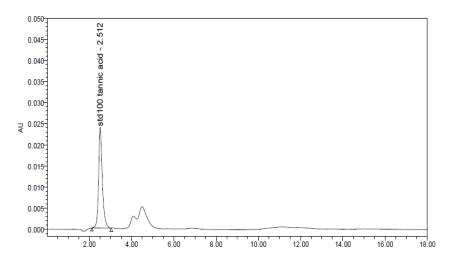
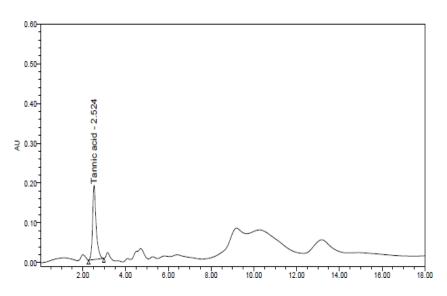


Figure 3. HPLC chromatogram of standard tannic acid.



**Figure 4.** HPLC chromatogram for tannic acid in *Quercus infectoria* (QI) galls extract.

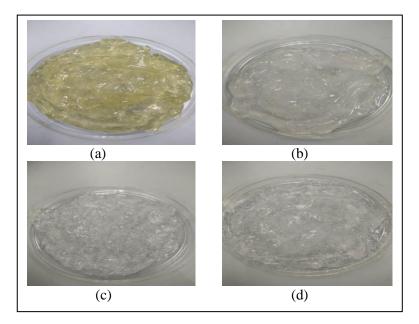
Four different gel formulations (F1, F2, F3 and F4) were prepared using different concentrations (0.5, 1, 1.5 and 2%) of Carbopol 940 polymer as is shown in table 2. Carbopol 940 was used as gelling agent in the formulation as it is biodegradable, bioadhesive, biocompatible, irritation free and not absorbed into body [13].

| Ingredients           | Compositions (%) |      |      |      |
|-----------------------|------------------|------|------|------|
|                       | F1               | F2   | F3   | F4   |
| Q. Infectoria extract | 0.02             | 0.02 | 0.02 | 0.02 |
| Propylparaben         | 0.1              | 0.1  | 0.1  | 0.1  |
| Carbopol 940          | 0.5              | 1.0  | 1.5  | 2.0  |
| Triethanolamine       | 1.5              | 1.5  | 1.5  | 1.5  |
| Distilled water (mL)  | 100              | 100  | 100  | 100  |

**Table 2**. The formulation gel with different concentration of carbopol 940.

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The physicochemical evaluation was optimized after preparing the gel with various concentrations of carbopol 940, where the 1.0 % of carbopol 940 containing gels was found to be compatible with the requirements of gel formulations as shown in the figure 2 (a), (b), (c), and (d) for their appearances with different concentration of Carbopol 940. For the physical appearance of four different concentrations of gelling agents, it was found that the formulation with 0.5% of carbopol 940 had changed its colour into yellowish after day one from the gel preparation. Moreover, it was a bit watery compared with other concentrations. The colour changes occurred because of the insufficient of carbopol 940 which is as a gelling agent. Insufficient of carbopol 940 would affect the viscosity value of that gel. Based on the viscosity theory, increase in viscosity of a semi-solid dosage form will lead to an increase in stability. Reasons for instability can be understood from the nature of immiscible phases and their interfacial properties because a gel cannot immobilize the droplet and the droplet can move that lead to the colour changes[14]. The best formulation of the herbosomal gel which is F2 was kept at varying condition of temperature. There was not much change of pH, viscosity, homogeneity and spreadability observed in this formulation.



**Figure 5.** The formulation of gel with different concentration of carbopol 940 for (a) 0.5%, (b) 1.0%, (c) 1.5%, and (d) 2.0%.

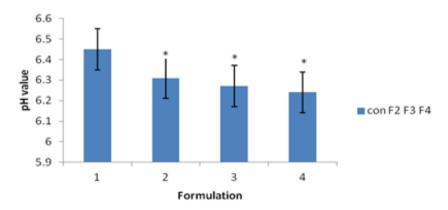
For the physical appearance study, it was showed that the formulation with 0.5% of carbopol 940 changed its colour into yellowish after one day of the gel preparation. Besides, this formulation was a bit watery as compared to other formulations. The colour changes occurred might due to the insufficient of carbopol 940 as gelling agent [1]. Insufficient of carbopol 940 can affect the viscosity of the gel. Based on the previous findings, it was revealed that increase in viscosity of a semi-solid dosage form will lead to an increase in stability [1]. Reasons for instability can be understood from the nature of immiscible phases and their interfacial properties because a gel cannot immobilize the droplet and the droplet can move that lead to the colour changes. From the study, it was revealed that the best formulation is F2 because this formulation showed not much change when stored at different condition and temperature.

The pH values of the herbosomal gel is found to be in the range from  $6.55 \pm 0.03$  to  $6.91 \pm 0.02$ , which was expected since the carbopol was formulated with pH between 5 to 5.5 and is neutralized using triethanolamine. The pH value showed that QI galls extract gel probably would not cause skin irritation. The QI galls extract gel was evaluated for its physical parameters such as colour, odour and homogeneity. The herbosomal gel formulation has a smooth texture and pale yellow transparent and homogenous and it has characteristic odour of QI galls extract. Table 2 shows data of the stability

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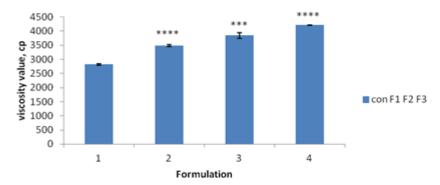
studies for antimicrobial herbosomal gel F2. Figure 7 shows the viscosity reading of the herbosomal gel, F2, for 3 consecutive weeks at for 3 different storage temperature. For the formulation with 1.5 and 2.0% of carbopol were found to be compatible to the gel formulation since the physical appearances was in good except the spreadability and viscosity parameters were not meet the requirements of the gel formulation as shown in table 2. This gel formulation was a bit thicker compared with the other concentrations. Therefore, it can be considered that these both concentrations were not giving a good physicochemical evaluation's result since the viscosity and spreadability gives indication of gel to spread on the skin part.

The formulations with 1.5 and 2.0% of carbopol, showed good physical appearance but the spread ability and viscosity did not achieve the gel formulation requirement as shown in table 2. These gel formulations were thicker and viscous as compared to other formulations. Therefore, it revealed that these formulations are not suitable to be developed as herbosomal gel as the physical appearance and viscosity were critical parameter in gel formulation. Four gel formulations (F1, F2, F3 and F4) that prepared using carbopol 940 were evaluated for physical appearance, pH, viscosity and spreadability. The findings showed that the data obtained (Refer table 4) were acceptable for gel formulations. The formulated herbosomal gels showed to be homogeneous, having good physical appearance and consistency. The pH values of all formulations were in acceptable range for gel formulation, pH (6.24-6.45) which is good for human skin. The results for pH determination were shown in figure 6.



**Figure 6.** pH value for gel formulation with different concentration of carbopol 940.

The Carbopol 940 was added as thickening gel in order to reach the gel requirements. The values of the viscosity were increased as the concentrations of the gelling agents were increased. Further the value between 2817.96 and 4213.42 centipoises which lies in the acceptable range for topical gel formulation in the figure 4 [15].

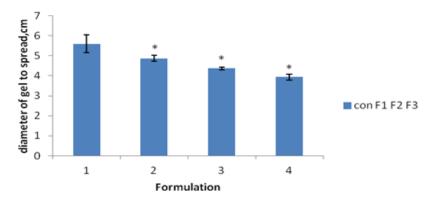


**Figure 7.** Viscosity value for gel formulation with different concentration of carbopol 940.

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Spreadability indicated the gel formulations are easily spreadable on the skin [4]. Among the gel formulations F1 to F4, F2 with 1.0% concentration of carbopol indicating that it has excellent spreadability which is 4.87cm diameter of the gel to spread compared with other formulations shown in the figure 8.



**Figure 8.** Spreadability value for gel formulation with different concentration of carbopol 940.

F2 was selected as the best herbosomal gel formulation and from now onwards, F2 will be known as F1. In stability study, two other formulations were made as control to observe their stability with different compositions. F2 was formulated without propylparaben as stabilizer and F3 was formulated without the addition of QI galls extracts. After all the formulations of herbosomal gel is completed, stability study was conducted by kept all the formulated gel at three different temperatures;  $45 \pm 2^{\circ}$ C,  $25 \pm 2^{\circ}$ C and  $4 \pm 2^{\circ}$ C for 21 days. In stability study, several testings were conducted such determination of pH value, viscosity, homogeneity and spreadability of the herbosomal gel formulation. The readings were taken for three consecutive weeks. Figure 6, 7 and 8 showed the findings from the stability study of herbosomal gel at 4°C, 25°C and 45°C respectively. Stability study at 4°C showed not much change in pH value, viscosity reading, homogeneity and spreadability throughout three weeks of experiments. The stability of herbosomal gel kept at 25°C was studied because room temperature is the most ideal temperature to store the herbosomal gel. The findings showed no significant changes as well.

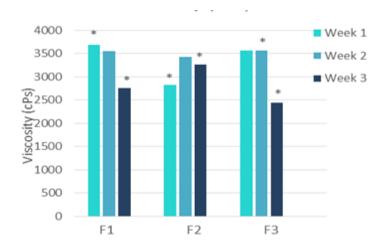


Figure 9. Viscosity of herbosomal gel at 4°C.

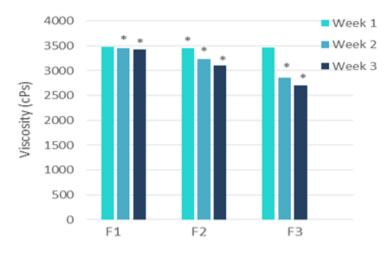


Figure 10. Viscosity of herbosomal gel at 25°C.

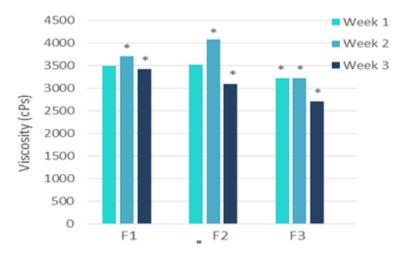
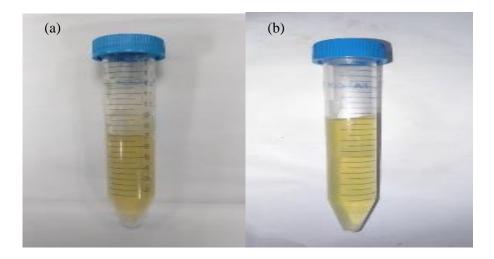


Figure 11. Viscosity of herbosomal gel at 45°C.

Viscosity of the QI galls herbosomal gel varies at different temperature. At 4°C, F1 is gradually decreasing in viscosity reading after three weeks of study. Viscosity of F2 is not consistent every week due to the absence of stabilizer to maintain its structure and stability which is propylparaben. At room temperature, 25°C, herbosomal gel F1, F2 and F3 shows no significant changes and consistent throughout the three weeks of stability study. F1 and F2 continue to show consistency when kept at 45°C after three weeks. However, F2 shows inconsistency in week 2 and week 3. Generally known that viscosity is affected by the storage temperature variations, so these variations are expected. Acceleration of chemical reactions, alteration of the activity of the active ingredients or components, viscosity, appearance, colour and odour can happen due to higher temperature [16]. Modifications in the formulations structure are not visually noticeable, thus further physical-chemical evaluation is necessary.

During stability study, the herbosomal gels were subjected to centrifugation test to identify its longterm stability. The samples were centrifuged at 3000rpm for 30mins at room temperature. After the centrifugation test is done, all formulated herbosomal gels kept in every temperature show no phase separation. Physical parameters testing was done after the centrifugation test. Centrifugation test is a direct procedure to evaluate the stability of the herbosomal gel when placed in a severe condition [17]. As there is no phase separation after the centrifugation test is done, it shows that the formulation of the herbosomal gel is stable over harsh condition. Figure 12 shows the herbosomal gel before and after the centrifugation test.



**Figure 12.** Herbosomal gel before and after centrifugation test, (a) before test and (b) after test.

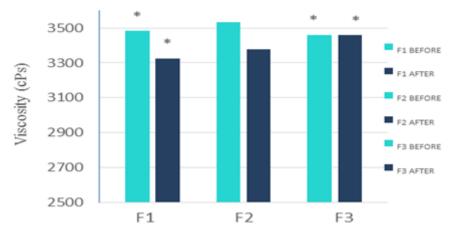


Figure 13. Viscosity for centrifugation test.

Viscosity reading of the herbosomal gel was recorded before and after the centrifugation test. This is to make there is no significant changes in the reading to maintain its stability [16]. However, viscosity reading for F2 which was a formulation without propylparaben has significant changes after the centrifugation test (Refer figure 13). Thus, this herbosomal gel from QI extracts need to have stabilizer to prolong its stability over time.

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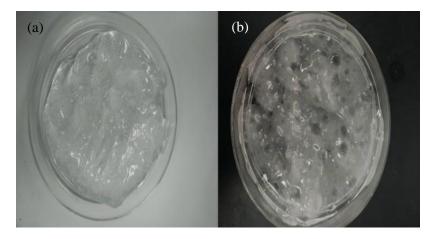
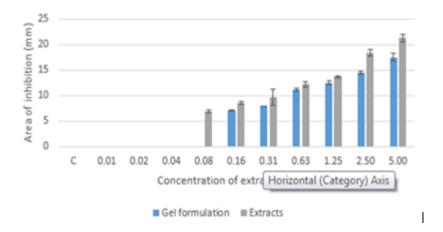
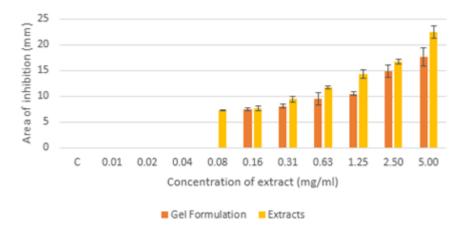


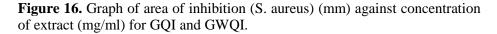
Figure 14. The formulation of antimicrobial gel (a) GWQI, (b) GQI.

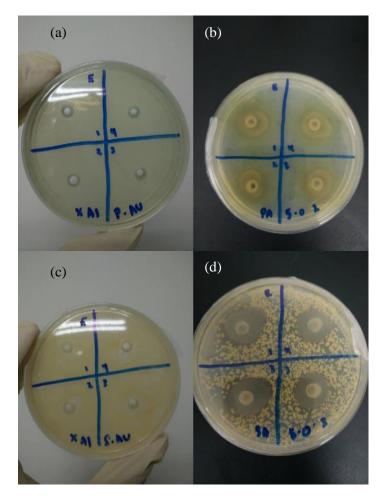
The gel was formulated with different concentration of QI galls extract. The concentration used in range of 0.01 mg/ml to 5.00 mg/ml using half-fold concentration calculation which resulted in concentrations of 0.01 mg/ml, 0.02 mg/ml, 0.04 mg/ml, 0.08 mg/ml, 0.16 mg/ml, 0.63 mg/ml, 1.25 mg/ml, 2.5mg/ml and 5.0mg/ml. The main constituent of QI galls extract is tannins which present 1794.18 mg/ml and minor constituents of free gallic acid about 76.22 mg/ml. Both components are responsible for antimicrobial activity. High amount of tannin implied that tannin is the active compound for antibacterial activity in study. Tannin is a phenolic that is soluble in water, alcohol and acetone and provides the precipitates with proteins [18]. The formulation of gel without active ingredient of QI galls extract (Refer figure 14) was formulated to test on the efficiency of QI galls extract as active ingredients to inhibit growth of bacteria. The gel was formulated with excipients such as paraben, triethanol amine and carbopol. Figure 15 and 16 below showed the graph of area of inhibition of the formulated gel against P.aeruginosa and S. aureus.

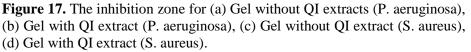


**Figure 15.** Graph of area of inhibition (P. aeruginosa) (mm) against concentration of extract (mg/ml) for GQI and GWQI.









The agar well diffusion method was carried out by bacteria (S. aureus or P. aeruginosa) spread through the surface of nutrient agar and treated with extract or gel formulation from different concentration which placed in the well bored with tip. The area of inhibition was taken using vernier

caliper in millimeter. The area took included the area of tip borer which was 5mm. Result showed that both gel formulation of QI galls extract, and extract of QI galls extract elicited antimicrobial activities as shown by presence of area of inhibition zones in well agar diffusion method. The antimicrobial effects of formulation from QI galls extract and extract of QI galls extract was dose-dependent as observed that area of inhibition zones increases with increase of concentration of extract.

The result of inhibition zones in figure 17 showed bacterial strains for S. aureus had bigger area than P. aeruginosa at comparable concentration of 5 mg/ml for both parameters. P. aeruginosa antimicrobial activity for gel formulation of QI galls extract was measured 17.57 mm whereas extract of QI galls extract was 21.29 mm. On the other hand, S. aureus, bactericidal effects for gel formulation of QI galls extract was 17.69 mm whereas whereas extract of QI galls extract was 22.47 mm. It demonstrated that agar well diffusion test gives significant difference in supporting dosedependency of QI galls extract extract on susceptibility of different strains of gram-bacteria. The plate that spread with gram-positive bacteria (S. aureus) has a greater antimicrobial activity compared gramnegative bacteria (P. aureginosa) in comparable concentration of extracts. Gram-negative bacteria have smaller area of inhibition compared to gram-positive bacteria due to present of lipopolysaccharides (LPS) layer on the surface of gram-negative bacteria which had high hydrophobicity and acts as strong barrier against hydrophobic molecules [19]. Consequently, lowering the ability of medication to absorb and pass through the barrier which decreasing the effect of antibacterial formulation gel on bacteria. The antibacterial formulation gel was able to penetrate call wall of gram-positive bacteria and more accessible than gram-negative bacteria due to presence of peptidoglycan and lack of outer membrane [19]. Furthermore, extract have higher affinity due to present of free gallic acid which increases the efficiency of QI galls extract.

The effectiveness of bactericidal between gel formulation of QI galls extract and extract of QI galls prone to depend on the structure and components present on the parameter. The concentration of extract commenced at different concentration range. Gel formulation of QI galls extract evoked at 0.16 mg/ml whereas extract of QI galls extracts at 0.08 mg/ml. The release rate of gel was slower than extract due to gel do not have a direct contact with extract. In virtue of gel formulation of QI galls extract made from gel, the extract effectiveness lowered due to extract necessarily pass through gel first before reaching the inner side of bacteria cell membrane. As for formulation of gel (Refer figure 14) without QI galls extract, the gel formulation was tested on both P. aeruginosa and S. aureus. Both plates exhibit zero area of inhibition. The plates were then contemplated with the plates which treated with formulated gel of QI galls extract. The differences in gowth of bacteria between formulation gel of QI galls extract as active ingredient [20]. Thus, effect of excipients such as paraben, triethanol amine and carbopol was negligible as there was no area of inhibition observed.

#### 4. Conclusion

From the study, it was revealed that the QI galls extract contains large amount of tannic acid which is 1794.18 mg/g and small amount of gallic acid which is 76.22 mg/g. For the physicochemical evaluation, the formulation of herbosomal gel consists of 1.0% of Carbopol 940 were found to be superior to the gel formulations since the physical appearances shows good properties. The reading pH value at 6.31 while the viscosity is at 3482.3144cps. Formulated gel showed good stability after 21 days of formulation, by not showing statistical differences in pH value, viscosity and spreadability before and after test. The antimicrobial testing evaluated by well diffusion method using P. aeruginosa is 17.75mm and S. aureus is 17.69mm. Hence, from all the results it was showed that QI galls extract was well incorporated into carbopol formulation to form herbosomal gel. This developed herbosomal gel using QI galls extract have good pH value, viscosity, spread ability, and stability against vary temperature and storage condition. Besides, the antibacterial activity of the both gel formulation and crude extract also exhibited a good and promising results. Hence, it can be concluded that the QI galls extract has a potential to be developed as a commercial antibacterial gel for medical use with further preclinical and long-term stability study can be conducted.

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