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Phytochemical profiling and antibacterial efficacy of *Artocarpus heterophyllus* seed-derived topical gel: A promising alternative towards ecofriendly healing

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Abstract

The utilization of medicinal plants as an alternative therapy has become necessary due to the current rise in antibiotic resistance and the high cost of conventional medical care. *Artocarpus heterophyllus*, a medicinal plant with demonstrated antimicrobial properties, represents a promising phytotherapeutic alternative to combat antimicrobial resistance. The present study was designed to develop and systematically evaluate a topical herbal gel incorporating seed extracts of *Artocarpus heterophyllus* with an emphasis on assessing its antibacterial efficacy and physicochemical characteristics. Following the extraction of the *Artocarpus heterophyllus* seed using ethanolic and hexane solvents (80%, v/v) for five days, their phytochemical content and antioxidant capacity were determined. Six herbal gel formulations were developed using the plant extracts, each incorporating 2% of a single gelling agent; carboxymethylcellulose, hydroxypropyl methylcellulose, or hydroxypropyl cellulose. The physicochemical parameters of the formulations were evaluated and the antibacterial potential was subsequently investigated. The yields of *Artocarpus heterophyllus* seed ethanolic and hexane extracts were 2.45% and 1.12%, respectively. The phytochemical examination of the extracts revealed the presence of tannins, alkaloids, saponins, flavonoids, terpenoids, polyuridine, steroids, reducing sugars, glycosides and anthraquinones. The extracts also demonstrated the significant presence of the antioxidant phytoconstituents with phenolic contents of 10.74 and 7.43 mg GAE/g, and flavonoid levels of 13.7 and 9.87 mg CE/g, in the ethanolic and hexane fractions, respectively. The characteristics of the developed formulations, including spreadability, pH, viscosity, and extrudability, were determined to be well within the limits. The antibacterial efficacy of the formulations was confirmed by inhibition zones of 21 mm and 17 mm against *Staphylococcus aureus* and *Bacillus cereus*, and 16 mm and 14 mm against *Escherichia coli* and *Pseudomonas aeruginosa*, respectively, with formulation F2 exhibiting the highest activity. These findings validate the antimicrobial potential of topical gel formulations incorporated with *Artocarpus heterophyllus* seed extracts, highlighting their potential as a viable phytotherapeutic agent.

Introduction

Artocarpus heterophyllus, commonly known as jackfruit, is a medicinally significant plant widely distributed across tropical regions, particularly in Southeast Asia and Brazil (Lima et al., 2014). Various parts of *A. heterophyllus* have been traditionally used to treat ailments such as asthma, ulcers, dermatitis, and cough (Mpiana, 2017), while its seeds are known for their therapeutic benefits in managing digestive and urinary disorders (Singh, 2018). The *Artocarpus heterophyllus* seeds exhibit significant nutritional and

functional potential; however, their utilization remains primarily confined to regional diets and food formulations such as gluten-free and starch-derived products (Madruga et al., 2014; Kaur et al., 2023; Kushwaha et al., 2023; Thatsanasuwan et al., 2023). The seeds of *Artocarpus heterophyllus* contain essential macronutrients and a diverse array of pharmacologically active compounds such as artocarpin, morin, and oxyresveratrol that are associated with antioxidant, anti-inflammatory, and antimicrobial activities (Wetprasit et al., 2000).

The growing global acceptance of traditional medicine, particularly in addressing antibiotic resistance, has emphasized the importance of exploring plant-derived therapeutic agents (Yuan et al., 2016; Gupta & Birdi, 2017). According to the World Health Organization (WHO), approximately 80% of the global population relies on herbal medicine for healthcare, and a significant number of essential medicines originate from plant-derived compounds (WHO, 2013; De Wet et al., 2013; Martínez & Barboza, 2010). The synergistic action of phytoconstituents in herbal extracts reduces the likelihood of microbial resistance development, making them promising candidates for pharmaceutical applications (Cheesman et al., 2017). Chronic wound infections pose a substantial clinical challenge due to the ability of organisms like *P. aeruginosa*, *S. aureus*, and *Enterococcus* spp. to establish biofilms that resist therapeutic intervention and promote infection persistence. Biofilm-associated bacteria are highly resistant to conventional antibiotics and topical treatments, including mupirocin and silver-based ointments, reducing their effectiveness. The flavonoid artocarpin, isolated from *Artocarpus hirsutus*, was demonstrated to effectively target multidrug-resistant Staphylococcus aureus, including biofilms (Meenu et al., 2022). Given that biofilm formation is implicated in 65% of microbial infections and up to 80% of chronic infections, alternative therapeutic approaches are essential. Plant-based extracts demonstrate promising antimicrobial activity by inhibiting biofilm formation and could serve as effective, natural alternatives to combat antimicrobial resistance and improve wound healing outcomes (Sitarek et al., 2020).

Topical drug delivery offers a targeted and effective method for administering bioactive compounds, with transdermal gels emerging as a preferred formulation due to their ease of application, biocompatibility, and enhanced drug release properties (Basha et al., 2011; Jayaraj et al., 2020). Topical gels demonstrate superior therapeutic efficacy and facilitate localized site-specific action while mitigating systemic exposure and related adverse effects (Helal et al., 2012; Manimaran & Nithya, 2014; Sudipta Das et al., 2011). Although *A. heterophyllus* seed extracts have been investigated for their nutritional properties and antimicrobial activity, their potential in wound healing formulations remains unreported.

This study hypothesizes that *Artocarpus heterophyllus* seed extracts possess the potential to be formulated into effective, stable, and antibacterial topical gel systems. To investigate this, a biphasic solvent extraction approach was employed to selectively isolate both hydrophilic and lipophilic phytoconstituents from *A. heterophyllus* seeds. The resulting extracts were subjected to comprehensive phytochemical and antioxidant profiling and subsequently incorporated into biopolymer-based gel formulations intended for topical delivery. These formulations were then evaluated for their physicochemical stability and antimicrobial activity against wound-associated pathogens.

Materials and Methods

Materials

Muller Hinton agar, Sodium Carboxymethyl cellulose, Hydroxypropyl methylcellulose, Hydroxypropyl cellulose, Dimethyl sulfoxide, Triethanolamine, 2,2-diphenyl-1-picrylhydrazyl, 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid, Ethanol, Hexane, Methanol and Trolox were obtained from HiMedia Laboratories, Mumbai, India. All other excipients/reagents used in the study were of analytical grade.

Seed collection and processing

The *Artocarpus heterophyllus* seeds were collected from the Southern part of India, specifically the Coimbatore district in Tamil Nadu. The seeds were washed with distilled water and allowed to dry in the shade for seven days at room temperature, without discarding the brown spermoderm. The dried samples were ground into flour using an electric grinder and thereafter stored at 4°C till further studies.

Extraction

The seed flour was subjected to extraction, wherein 25 g of the samples were macerated in two different solvents, 80% (v/v) ethanol and absolute hexane. Ethanol was chosen to extract polar compounds like phenolics and flavonoids, while hexane selectively extracted lipophilic compounds such as terpenoids and fatty acids, which are known to possess significant antioxidant and antimicrobial activity (Dai & Mumper, 2010). The samples were then incubated for five days with intermittent shaking at room temperature. The samples were filtered through Whatman filter paper (Grade 1), and the filtrate was incubated in a 45°C water bath (Karthy et al., 2009). The samples were allowed to concentrate, and thereafter, the extraction efficiency was established through determining the dry weight of the processed sample (Gaire et al., 2011). The extracts were transferred into sterile containers and stored at 4°C until further.

$$\text{Extraction efficiency} = \frac{\text{Final dry weight}}{\text{Initial dry weight}} \times 100$$

Two different concentrations of each extract, ethanol, and hexane were prepared at 500 mg/mL and 1000 mg/mL in 10% (w/v) Dimethyl sulfoxide (DMSO). These concentrations were selected based on preliminary solubility tests and the need to evaluate the effects of extracts at concentrations relevant to typical phytochemical assays (Gul et al., 2017).

Phytochemical screening

The phytochemical analysis of the extracts was determined for tannins, alkaloids, saponins, flavonoids, terpenoids, anthraquinones, glycosides, polyuronides, steroids, reducing sugar, and amino acids (Odebiyi & Sofowora, 1978; Gul et al., 2017; Bhat et al., 2017).

Antioxidant assay

Estimation of antioxidant content

The estimation of antioxidant content was assessed by the determination of total phenolic and flavonoid content of the extracts. The total phenolic content was determined following the Folin–Ciocalteu colorimetric method (Kassegn, 2018). The extract sample of 0.01 mL (5 mg/mL) was mixed with 0.2 mL of Folin–Ciocalteu reagent and 1.39 mL of distilled water. The solution was incubated at room temperature for three min, followed by the addition of 0.4 mL sodium carbonate (20%, w/v) and re-incubation under the same conditions for 20 min. The absorbance values of the samples were measured at 760 nm with a UV Vis spectrophotometer (Shimadzu). All measurements were carried out in triplicate (n = 3) to ensure reproducibility. The gallic acid standard curve was used to determine the extracts' total phenolic content, which was then expressed in milligrams of gallic acid equivalent (GAE) per gram of extract.

The flavonoid content estimation was carried out with 0.1 mL of the extract mixed with 1.4 mL of distilled water, followed by 0.03 mL of sodium nitrate (5%, w/v). The solution was incubated for five min at room temperature and thereafter was supplemented with 0.2 mL of aluminum trichloride (10%, w/v). The samples were further incubated for five min at room temperature and subsequently mixed with 0.2 mL of 10% NaOH and 0.24 mL of distilled water. The absorbance values were measured at 510 nm in a spectrophotometer, and the flavonoid content was determined employing catechin as the standard. All measurements were performed in triplicate (n = 3) to ensure accuracy and reproducibility. The obtained values were expressed as milligrams of catechin equivalent (CE) per gram of extract (Jahromi, 2019).

Determination of antioxidant activity

The antioxidant activity was evaluated through the ability of the extracts to scavenge free radical 2,2-diphenyl-1picrylhydrazyl (DPPH), hydroxyl radical scavenging ability, and ferric ion reducing capacity.

DPPH Assay

The DPPH free radical scavenging activity was determined through the addition of 4.5 mL of the said reagent (0.002%, v/v in ethanol) into the tubes containing 0.5 mL of the extract samples at different concentrations (200-6.25 µg/mL). The samples were incubated for 30 min at room temperature in the dark. Ascorbic acid was employed as the standard solution, and the absorbance values of the samples, standard, and control (ethanol) were measured using a spectrophotometer. All measurements were conducted in triplicate (n = 3) to ensure reproducibility. The antioxidant activity of the extract was calculated as given below (Mensor et al., 2001)

$$\text{AA \%} = \frac{(\text{Abs Control} - \text{Abs Sample}) \times 100}{\text{Abs Control}}$$

ABTS assay

Artocarpus heterophyllus seed extracts were investigated for their ability to scavenge ABTS (2, 2'-azinobis (3-ethylbenzthiazoline)-6-sulphonic acid). The ABTS reagent constituted of 7 mM

ABTS and 2.45 mM potassium persulphate were prepared and allowed to stand at room temperature in the dark for 12 to 16 h prior to use. Thereafter, 0.3 mL of the reagent was mixed with 0.5 mL of the extract samples at different concentrations (200-6.25 µg/mL), and the final volume was made up to 1.0 mL with ethanol. Likewise, the Trolox standard was also prepared at different concentrations (200-6.25 µg/mL) and mixed with the reagent, while ethanol was employed as the control. The absorbance was measured at 745 nm after six min, and the previously mentioned formula was used to determine the percentage of inhibition in the scavenging activity (Shirwaikar et al., 2004). All measurements were performed in triplicate (n = 3) to ensure accuracy and consistency.

Ferric Reducing Antioxidant Power (FRAP)

The reducing potential determination was carried out by preparing 0.5 mL of the extracts, constituting different concentrations (2000, 1000, 500, 250, and 125 µg/mL) in methanol. The samples were then supplemented with 1 mL potassium phosphate buffer (0.2 M, pH 6.6) and 1 mL of aqueous potassium hexacyanoferrate ($K_3Fe(CN)_6$, 1% v/v), followed by incubation at 50 °C in a water bath for 30 min. Thereafter, 1 mL of trichloroacetic acid solution (10%, v/v) was added and centrifuged for 10 min at 5000 rpm, and 1.5 mL of the supernatant was mixed with an equal volume of distilled water. Thereafter, 0.1 mL of 1% $FeCl_3$ solution (v/v in ethanol) was added and the absorbance values were determined at 700 nm. All measurements were conducted in triplicate (n = 3) to ensure reliability. The assay utilized catechin as the standard metal reductant and methanol as the control (Rechek et al., 2021).

Table 1. Percentage composition of novel gel formulation.

S.NO	INGREDIENTS	F1	F2	F3	F4	F5	F6
1.	Sodium Carboxymethylcellulose	2	-	-	2		
2.	Hydroxypropyl methylcellulose	-	2	-	-	2	-
3.	Hydroxypropyl cellulose	-	-	2	-	-	2
4.	Ethanol extract	20	20	20	-	-	-
5.	Hexane extract	-	-	-	20	20	20
6.	Glycerin	8	8	8	8	8	8
7.	Oleic acid	5	5	5	5	5	5
8.	Water (mL) make upto	100	100	100	100	100	100

Formulation development of *Artocarpus heterophyllus* seed extract

The topical gel formulation utilizing *Artocarpus heterophyllus* seed extract was developed with three different gel bases, Sodium Carboxymethylcellulose (Na CMC), hydroxypropyl methylcellulose (HPMC), and hydroxypropyl cellulose (HPC) (da Silva et al., 2022). Each of these bases was incorporated independently in all formulations of the gel in tandem with the ethanolic and hexane extracts. Additionally, all the formulations uniformly constituted of oleic acid (5%, v/v) and glycerin (8%, v/v) employed as solubilization agents (Naso et al., 2021) and humectants (Chen et al., 2022), respectively. Table 1 exhibits the compositions that were employed in the preparation of the gel formulations.

The gel bases were dispersed in half of the total water and stirred for 20 min. Thereafter, glycerin was introduced at the end of the dispersion stage. The seed extracts were then added gradually, and the solution was mixed thoroughly. Subsequently, the solution was supplemented with oleic acid, and the final volume was adjusted to 100% with distilled water.

Evaluation of the gel formulation

Organoleptic properties

The homogeneity, consistency, odor, phase separation, and overall appearance of the formulations were examined (Chiang et al., 2009).

pH

A digital pH meter was used to measure the gel's pH with accuracy.

Viscosity

The viscosity of the developed formulation was assessed by employing a Viscometer. The gel sample weighing 10 g was placed in a 50 mL beaker, followed by which a spindle groove was dipped and allowed to run. The readings were recorded after 3 min intervals in triplicate (Welin-Berger et al., 2001). Each formulation was tested in triplicate (n = 3) to ensure consistency and reproducibility

Spreadability

The topical gel's spreadability was determined by compressing the 0.5 g gel samples between glass plates of predetermined weight. The diameter of the gel's spread was measured at various intervals after a 100 g weight was applied to the slides for 10 min. The spreadability was calculated using the formula,

$$\text{Spreadability (S)} = \text{M} \times \frac{L}{\text{T}}$$

Wherein, M was the weight that is placed on the upper slide, L is the length of the glass slide, and T represents the time duration (Garg et al., 2002). Each formulation was tested using three independent samples (n = 3), and the measurements were conducted in triplicate to ensure reproducibility.

Determination of formulation stability

The gel formulations were subjected to physical stability analysis under different storage conditions pertaining to 40 ± 2 °C/ 75 ± 5% RH, 30 ± 2 °C/ 65 ± 5% RH, and 25 ± 2 °C/ 60 ± 5% RH for 28 days. The overall stability was examined by assessing for variation in extrudability, physical appearance, and phase separation of the gel. About 10 g of gel formulations were packed tightly into a closed, collapsible tube, which had a crimped end, and the roll back flow was stopped by employing a clamp. The cap was removed to extrude the gel, and then the amount of gel extruded was measured as a percentage (Rajasekaran et al., 2016).

$$\text{Extrudability (\%)} = \frac{\text{Amount of ointment extruded from tube}}{\text{Total amount of ointment in the tube}} \times 100$$

The physical appearance of the gel formulations was assessed through examination of color, appearance (transparency), homogeneity, and grittiness. Further, the gel formulations were also evaluated for phase separation (Alam et al., 2023). All observations and measurements were performed in triplicate to ensure reproducibility.

Application of the gel formulation

The application of the developed gel formulation was determined by evaluating its antimicrobial potential against common wound infection-causing pathogens. The antibacterial activity of the formulation was tested against *E. coli* (MTCC 294), *P. aeruginosa* (MTCC 1034), *S. aureus* (MTCC 1430), and *B. cereus* (MTCC 1306) using the well diffusion assay. Gel formulations at a standardized concentration of 0.1 g/mL were added to culture-swabbed wells in Mueller-Hinton agar plates and incubated at 37°C for 24 h. A 0.5 McFarland turbidity

standard was prepared to ensure consistent inoculum concentration, and the turbidity bacterial suspension was adjusted to match this standard using a spectrophotometer. Three independent replicates (n = 3) were performed per formulation for each microorganism to ensure statistical reliability.

To assess the specific antimicrobial contribution of the *Artocarpus heterophyllus* seed extract, a control formulation was prepared using 1% each of sodium carboxymethyl cellulose, hydroxypropyl methylcellulose, and hydroxypropyl cellulose, along with 5% glycerin and 8% oleic acid, without the extract. The control gel was included in the assay under the same conditions to compare its effect with the formulated gels. Gentamicin (10 µg/disc) was incorporated as a positive control to facilitate the comparison of the antibacterial effects. The zone of inhibition exhibited against each culture by different formulations, including the control, was recorded (Themozhil et al., 2007).

Statistical analysis

All experiments were performed in triplicate (n = 3), and the results are expressed as mean ± standard deviation (SD).

Results and Discussions

Percentage yield of extracts

The *A. heterophyllus* seeds subjected to ethanolic and hexane extraction resulted in yield percentages of 2.45% and 1.12%, respectively. The ethanolic extract had a higher yield than that of the hexane solvent. This observation may be due to the increased solubility of the phytochemicals and other constituents of the plant in ethanol as compared to hexane. This suggested that ethanolic solvent had a high extraction potential, and this is also supported by previous studies, which also reported ethanol as a more efficient solvent (Eve et al., 2020; Rathi et al., 2015; Gupta, et al., 2011).

Phytochemical analysis of the extracts

The phytochemical screening of alcoholic and hexane extracts from *A. heterophyllus* seeds was depicted in Table 2. The analysis confirmed the presence of tannins, alkaloids, saponins, flavonoids, terpenoids, polyuridine, steroids, and reducing sugars in both extracts. Furthermore, the ethanolic extract demonstrated the presence of glycosides, whereas the hexane extract exhibited the occurrence of anthraquinones. The phytochemicals showed a range of potential activities that could be implemented for various medicinal applications. For example, as previously reported, the medical properties of saponins, such as their antispasmodic action and toxicity toward cancer cells, are well established. Furthermore, alkaloids show pharmacological, cytotoxic, antispasmodic, antibacterial, anti-inflammatory, and antimalarial properties. Steroids have insecticidal, antimicrobial, and cardiotonic effects. Tannins aid in the healing of burns, hemorrhoids, varicose ulcers, and frostbite. The ability of flavonoids to scavenge free radicals demonstrates their antioxidant effects (Bhat et al., 2017).

Table 2. Phytochemical investigation of *A. heterophyllus* seed extract.

S. NO	PHYTOCHEMICAL ANALYZED	ETHANOLIC EXTRACT	HEXANE EXTRACT
1.	Tanins	+	+
2.	Alkaloids	+	+
3.	Saponins	+	+
4.	Flavanoids	+	+
5.	Anthraquinones	-	+
6.	Terpenoids	+	+
7.	Glycosides	+	-
8.	Polyurinides steroids	+	+
9.	Reducing sugar	+	+
10.	Amino acids	-	-

+ = Positive, - = Negatives

Antioxidant assay

Estimation of antioxidant content

The total phenolic content of the ethanolic and hexane extracts of *A. heterophyllus* seeds was estimated using the gallic acid standard curve and was found to be 10.74 mg and 7.43 mg of GAE/g of extract. The total phenolic content was found to be higher in the ethanolic extract. The phenolic compounds significantly enhanced the antioxidant properties due to their high redox potential, enabling them to adsorb and neutralize free radicals, quench singlet and triplet oxygen, as well as decompose peroxides (Sahu, Kar, & Routray, 2013). Additionally, they also showed significant antimicrobial properties, such as antiviral, antifungal, and antimicrobial capabilities. Additionally, it has been demonstrated that they provide anti-inflammatory and anti-obesity attributes (Sitarek et al., 2020).

Similarly, for the ethanolic and hexane extracts, the total flavonoid concentration was determined to be 13.7 mg and 9.87 mg of CE/g of extract, respectively. As discussed in the above section, the flavonoids exhibit antioxidant effects, through inhibition of reactive oxygen species production (Bhat et al., 2017). Further, they have also been revealed to show antimicrobial properties with potential action against bacterial cell membranes, which has been evidently demonstrated against methicillin resistant *Staphylococcus aureus,* wherein they tend to increase the membrane permeability (Wu et al., 2019).

Determination of antioxidant activity

The most notable antioxidant activity seen was the ability to scavenge hydroxyl radicals, which is followed by hydrogen peroxide and ferrous iron chelation (Biworo et al., 2015). DPPH is widely used to test the ability of compounds to act as free radical scavengers or hydrogen donors, and to evaluate antioxidant activity of

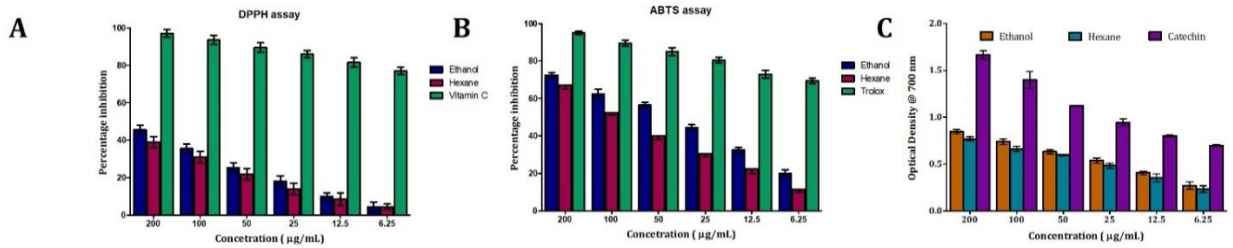

Figure 1. Determination of antioxidant activity. A. DPPH assay of the extracts, **B.** ABTS assay of the extracts and **C.** Ferric reducing power assay of the extracts. Values are expressed as mean ± standard deviation (SD), n = 3. Error bars represent standard deviation. Statistical significance was determined by one-way ANOVA with $p < 0.05$ considered significant.

food. DPPH is frequently used for determining a compound's capacity to donate hydrogen or scavenge free radicals, as well as to assess the antioxidant activity of food. In recent years, it has also been applied to measure antioxidants in intricate biological systems (Lee et al., 2007).

DPPH assay

The free radical activity through DPPH assay of both ethanolic and hexane extracts of *A. heterophyllus* seeds was shown in Figure 1a. An increase in extract concentration was found to considerably increase the inhibition percentage, and different extract demonstrated varying degrees of activity. The ethanolic extracts fraction exhibited a higher inhibition percentage compared to the hexane. The scavenging rates of ethanolic extracts to DPPH were 46 ± 1.2 %, 36 ± 1.1 %, 27 ± 0.9 %, 18 ± 0.8 %, 10 ± 0.5 %, and 5 ± 0.3 % at concentrations of 200, 100, 50, 25, 12.5 and 6.25 µg/mL, respectively. Similarly, the hexane extracts produced scavenging rates of 39 ± 1.0 %, 31 ± 0.9 %, 22 ± 0.8 %, 14 ± 0.6 %, 8 ± 0.5 %, and 3 ± 0.2 % at concentrations of 200, 100, 50, 25, 12.5, and 6.25 µg/mL, respectively. The IC_{50} determined through linear regression analysis value for the DPPH scavenging by the *A. heterophyllus* seeds extracts are 222.22 µg/mL ($R^2 = 0.96$) and 256.09 µg/mL ($R^2 = 0.98$) for the ethanolic and hexane extracts, respectively. This aligns with previous findings, where IC_{50} values of the seed extract from *A. heterophyllus* between 70-250 µg/mL (Loizzo et al., 2010), 199.12 µg/ml (Kandel et al., 2019), 410 µg/mL (Soubir, 2007), 398 µg/mL (Chandran, 2017), 636-715 µg/mL (Gupta, et al., 2011), 643-786 µg/mL (Shanmugapriya et al., 2011) and 300-500 µg/mL (Rechek et al., 2021).

ABTS assay

The ABTS scavenging assay can be used to screen antioxidants that are hydrophilic or lipophilic. The percentage inhibition of ABTS radical cations by ethanolic and hexane extracts of *A. heterophyllus* seeds is shown in Figure 1b. The scavenging rates of ethanolic extracts to ABTS were 71 ± 1.4%, 60 ± 1.2%, 55 ± 1.1%, 43 ± 0.9%, 31 ± 0.8%, and 22 ± 0.6% at concentrations of 200, 100, 50, 25, 12.5, and 6.25 µg/mL, respectively. Similarly, the hexane extracts produced scavenging rates of 65 ± 1.3%, 54 ± 1.1%, 38 ± 0.9%, 29 ± 0.7%, 20 ± 0.6%, and 13 ± 0.5% at concentrations of 200, 100, 50, 25, 12.5 and, 6.25 µg/mL, respectively. The IC_{50} values determined through linear regression analysis for the ABTS scavenging by the *A. heterophyllus* seeds extracts are 140.84 µg/mL and 153.84 µg/mL for the ethanolic and hexane extracts, respectively. The other studies have reported an IC_{50} value of between 49-55 µg/mL (Gupta, et al., 2011) and 290-500 µg/mL (Shanmugapriya et al., 2011).

Ferric reducing power

Alternatively, the ferric reducing power was employed to ascertain the reduction potential of *A. heterophyllus* seed extracts. The reduction of the Fe^{3+}/ ferricyanide complex to the ferrous form occurs in this assay due to antioxidant activity. The ferric reducing power of the extracts was associated with reductants that facilitate antioxidant action through donation of electrons and subsequent reaction with free radicals to transform them into more stable compounds (Rechek et al., 2021). As shown in Figure 1c, an increased level of reducing potential was found to be correlated with an increasing concentration of the *A. heterophyllus* seed extracts. However, the reducing capacity of the extracts was observed to be comparable to, or in some cases slightly higher than, the catechin standard under the experimental conditions. The results revealed the reducing potential of 21.43 µg/mL for the ethanolic extract, 28.61 for the hexane extract and 3.6 µg/mL for the catechin at $A_{0.5}$. The other reports indicate a reducing potential of 14-16 µg/mL (Gupta, et al., 2011) and 9-13 µg/mL (Shanmugapriya et al., 2011). The presence of a reducing agent facilitates the donation of hydrogen from phenolic compounds, which is responsible for the ability to decrease Fe^{3+} (Duh, 1998). Additionally, phenolic compounds' antioxidant activity is influenced by the number, and location of their hydroxyl groups (Shimada et al., 1992).

Development of *Artocarpus heterophyllus* seed extract formulation

The formulation development process utilized exclusively pharmaceutical-grade ingredients and was

produced with the composition scheme provided in Table 1. The varying concentrations of Na-CMC, HPMC, and HPC as gelling agents, the ethanolic and hexane extracts of *A. heterophyllus* seed as the active ingredient, oleic acid as a solubilization agent and glycerin as the humectant. The developed gel formulation is displayed in Figure 2.

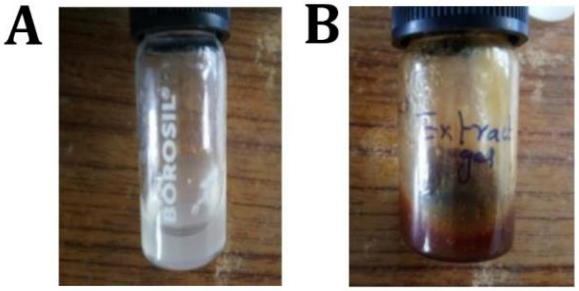

Figure 2. Developed gel formulation. **A**. Blank gel without the extracts, **B**. Gel formulation encompassing extract.

Evaluation of the gel formulation

Organoleptic properties

The developed gel formulation's physicochemical analysis in terms of overall appearance, phase separation, odor, homogeneity, and consistency was provided in Table 2. The color of the formulation was amber to brown with a translucent appearance, and also demonstrated grit as well as lump free consistency. Furthermore, it was determined that the developed formulation is homogeneous and stable, demonstrating no signs of phase separation.

pH

The pH values of all the formulations were found to range from 6.20 ± 0.05 to 5.29 ± 0.04 (Figure 3a), which are considered suitable for avoiding skin irritation upon application (Lucero et al., 1994). The typical pH level of the skin is relatively acidic, enabling it to maintain the microbiota and skin homeostasis. The skin's acidic mantle disturbance allows harmful bacteria to proliferate and lead to detrimental conditions. Consequently, it is recommended to use skincare and makeup products with a low acidic pH to preserve healthy skin (Danby & Cork, 2018; Panther & Jacob, 2015).

Viscosity

A significant physical characteristic of topical formulations that influences the rate of drug release is their viscosity; typically, a higher viscosity would result in a more rigid structure and a lower rate of drug release. The viscosity amidst various formulations were observed to range between 8878 ± 45 to 7400 ± 38 cps as displayed in Figure 3b. Viscosity of a semi-solid formulation may impact skin retention of the dosage form and drug delivery/penetration via the skin. The viscosity of a semi-solid formulation can influence the extent to which the medication penetrates the skin and persists in the correct dosage form (Ramezanli & Michniak-Kohn, 2018).

Spreadability

The spreadability values displayed in Figure 3c revealed that gels produced with all of the polymers utilized dispersed slightly upon the application of shear. The highest spreadability was exhibited by the hydroxypropyl methylcellulose (F2) with 5.38 ± 0.06 cm, whereas the lowest was that of 4.60 ± 0.04 cm for the hydroxypropyl cellulose (F6). Spreadability is crucial since it demonstrates precisely how the gel behaves once it is extruded from the tube. The effectiveness of topical therapy, and the administration of a standard dose of a medicinal formulation to the skin is significantly influenced by the gel's ability to distribute evenly over the skin (Chen et al., 2016).

Determination of formulation stability

The development of a stable topical emulsion necessitates the sustained and prolonged release of antioxidants to maintain efficacy throughout the duration of storage. Environmental stressors such as humidity and temperature can have an impact on the stability of an emulsion. These factors could result in physical and chemical alterations of formulations arising

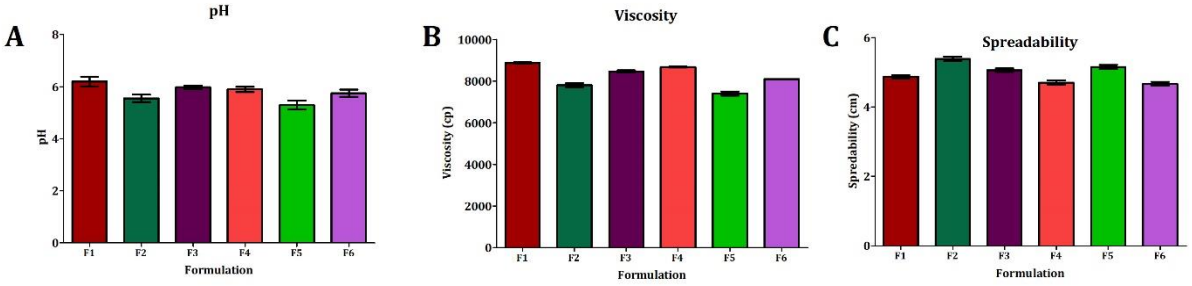

Figure 3. Evaluation of the gel formulation. **A.** pH of the developed formulations, **B.** Viscosity of the developed formulations and **C.** Spreadability of the developed formulations. Values are expressed as mean ± standard deviation (SD), n = 3. Error bars represent standard deviation. Statistical significance was determined by one-way ANOVA with $p < 0.05$ considered significant.

from several aspects like extrudability, color, appearance, homogeneity, grittiness, and phase separation, thereby indicating the degradation of the active component in the formulation. The stability of the developed gel formulation was evaluated based on its extrudability, physical appearance, and phase separation. The results are presented in Table 3. Gel formulations with extrudability percentages exceeding 90% were deemed excellent, 80% were classed as good, and 70% were considered fair. The different formulations can be arranged based upon their extrudability in the following order: F2>F3>F5>F4>F1>F6. Since the formulation's viscosity and extrudability are intimately related, extrudability can also be defined as the force needed to extract the ointment from the tube. The extrudability measurements also demonstrated the formulation's tendency to become stiffer, and this could be attributed towards the nature of fatty acid moieties. Higher concentrations of unsaturated fatty acids may enhance extrudability due to their capacity to reduce viscosity (Ilievska et al., 2016). Since the study has utilized a constant concentration of the fatty acids throughout the formulations, the extrudability reported could be connected with the interaction between *A. heterophyllus* seed extract type and the gelling agents. Throughout the incubation period, the developed formulation's color remained evenly amber, its translucent aspect persisted, and there were no alterations to its homogeneity or grittiness. One of the factors altering the product's color is the oxidation reaction (Ansel et al., 1990).

Phase separation occurs when smaller dispersed phase globules merge into substantially larger ones. Due to density differences, these larger globules either settle down (sedimentation) or rise up (creaming). The developed formulations exhibited no phase separation, thus rendering them exceptionally stable in a variety of storage settings. Therefore, the data indicate that there are no significant variations in droplet size caused by instability phenomena such as coalescence, which may lead to the two phases' gravitational separation and eventual emulsion collapse (Yang et al., 2013).

Application of gel formulations

Antibacterial activity of all the prepared formulations was carried out against *E. coli*, *P. aeruginosa*, *S. aureus,* and *B. cereus*, wherein it was

Table 3. Physical stability examination of the developed gel formulations.

DAY	40 ± 2°C/ 75 ± 5% RH			30 ± 2°C/ 65 ± 5% RH			25 ± 2°C/ 60 ± 5% RH		
				F1					
	EXT	PA	PS	EXT	PA	PS	EXT	PA	PS
0	Good	NC	No	Good	NC	No	Good	NC	No
7	Fair	NC	No	Good	NC	No	Good	NC	No
14	Fair	NC	No	Fair	NC	No	Fair	NC	No
21	Fair	NC	No	Fair	NC	No	Fair	NC	No
28	Fair	NC	No	Fair	NC	No	Fair	NC	No
				F2					
	EXT	PA	PS	EXT	PA	PS	EXT	PA	PS
0	Excellent	NC	No	Excellent	NC	No	Excellent	NC	No
7	Excellent	NC	No	Excellent	NC	No	Excellent	NC	No
14	Excellent	NC	No	Excellent	NC	No	Excellent	NC	No
21	Excellent	NC	No	Excellent	NC	No	Excellent	NC	No
28	Good	NC	No	Excellent	NC	No	Excellent	NC	No
				F3					
	EXT	PA	PS	EXT	PA	PS	EXT	PA	PS
0	Excellent	NC	No	Excellent	NC	No	Excellent	NC	No
7	Excellent	NC	No	Excellent	NC	No	Excellent	NC	No
14	Excellent	NC	No	Excellent	NC	No	Excellent	NC	No
21	Good	NC	No	Excellent	NC	No	Excellent	NC	No
28	Good	NC	No	Good	NC	No	Good	NC	No
				F4					
	EXT	PA	PS	EXT	PA	PS	EXT	PA	PS
0	Good	NC	No	Good	NC	No	Good	NC	No
7	Good	NC	No	Good	NC	No	Good	NC	No
14	Fair	NC	No	Good	NC	No	Good	NC	No
21	Fair	NC	No	Fair	NC	No	Fair	NC	No
28	Fair	NC	No	Fair	NC	No	Fair	NC	No
				F5					
	EXT	PA	PS	EXT	PA	PS	EXT	PA	PS
0	Excellent	NC	No	Excellent	NC	No	Excellent	NC	No
7	Excellent	NC	No	Excellent	NC	No	Excellent	NC	No
14	Excellent	NC	No	Excellent	NC	No	Excellent	NC	No
21	Good	NC	No	Good	NC	No	Excellent	NC	No
28	Good	NC	No	Good	NC	No	Good	NC	No
				F6					
	EXT	PA	PS	EXT	PA	PS	EXT	PA	PS
0	Good	NC	No	Good	NC	No	Good	NC	No
7	Fair	NC	No	Fair	NC	No	Good	NC	No
14	Fair	NC	No	Fair	NC	No	Fair	NC	No
21	Fair	NC	No	Fair	NC	No	Fair	NC	No
28	Fair	NC	No	Fair	NC	No	Fair	NC	No

*EXT- Extrudability, PA- Physical appearance, PS-Phase separation, NC- No change

found to exhibit significant zone of inhibition as depicted in Table 4. Among the formulations, F2 exhibited the highest activity, with inhibition zones of 21.0 ± 0.9 mm against *S. aureus* and 17.0 ± 0.5 mm against *B. cereus*. Similarly, it showed zones of 16.0 ± 0.8 mm for *E. coli* and 14.0 ± 0.6 mm for *P. aeruginosa* at a standardized concentration of 0.1 g/mL, indicating superior antibacterial efficacy. In comparison, the control formulation, consisting of the gel base without the extract, exhibited minimal antibacterial activity, with zones of inhibition of 2.0 ± 0.2 mm for *E. coli* and 1.0 ± 0.1 mm for *P. aeruginosa*, and no significant activity for *S. aureus* and *B. cereus*. The positive control, gentamicin, demonstrated zones of inhibition of 10.0 ± 0.3 mm for *E. coli*, 12.0 ± 0.5 mm for *P. aeruginosa*, 8.0 ± 0.4 mm for *S. aureus*, and 6.0 ± 0.3 mm for *B. cereus*. This clearly showed the contribution of the *Artocarpus heterophyllus* seed extract to the antibacterial properties of the gel formulations.

Thus, it can be concluded that the gel formulation that was generated, containing extracts of *A. heterophyllus* in both ethanolic and hexane forms, clearly shows antibacterial activity. Different bioactive components in the seed may account for the differential in antibacterial activity between the two crude extracts (ethanolic and hexane). The seeds included a variety of bioactive substances, such as alkaloids, steroids, terpenoids, anthraquinones, reducing sugars, glycosides, bioactive compounds, and flavonoids that are reported to have antimicrobial property (Mpiana, 2017). These substances have also been linked in previous reports to having antiviral, antibacterial, anthelminthics, anti-inflammatory, and antifungal properties (Mandal et al., 2005; Chandrika et al., 2004; Arung et al., 2007).

The antibacterial activity of *A. heterophyllus* seed extracts was evaluated in previous studies, revealing significant inhibition against both Gram-negative and Gram-positive bacteria. The methanolic extract exhibited the highest inhibitory effect on *K. pneumoniae* (19 mm), while the aqueous extract demonstrated maximum inhibition against *S. aureus* (16 mm) (Bhat et al., 2017). Their activity against foodborne pathogens exhibited inhibitory effects, except against *B. cereus*. The total water extract showed the highest inhibition against *S. aureus* (15 mm), while the ethyl acetate fraction exhibited significant activity against *S. enterica* (13 mm). The aqueous fraction displayed notable inhibition against *L. monocytogenes* (15 mm) and E. faecalis (13 mm) (Loizzo et al., 2010). Significant antibacterial activity was observed for both ethanolic and hexanolic extracts against clinical isolates of multidrug-resistant *P. aeruginosa*, methicillin-resistant *Staphylococcus aureus* (MRSA), and methicillin-susceptible *S. aureus* (MSSA), with inhibition zone diameters ranging from 8.5 ± 0.5 mm to 16.5 ± 0.25 mm (Eve et al., 2020). Further, antibacterial screening of the methanolic seed extracts revealed zones of inhibition against *Proteus mirabilis* and *Salmonella enterica typhi,* measuring 6.66 ± 1.15 mm and 8.33 ± 1.52 mm, indicating moderate bacteriostatic activity (Kandel et al., 2019).

Conclusion

The developed topical gel formulation containing 20% of the *Artocarpus heterophyllus* seed extract demonstrated considerable activity against the pathogens. Therefore, this suggests the release of herbal components from the prepared gel matrix. The pro- and anti-inflammatory activities observed in the extracts suggest potential therapeutic applications for inflammatory skin conditions, but these effects may vary depending on dose and specific conditions, necessitating further studies to better understand the dose-response dynamics. Furthermore, the natural constituents of the extract may exert modulatory effects on bacterial resistance mechanisms, such as adhesion and penetration into host tissues; however, further investigation is needed to confirm these effects.

Conflicts of interest

The author(s) declare that they have no known competing financial or non-financial, professional, or personal conflicts that could have appeared to influence the work reported in this paper.

Table 4. Zone of inhibition of the developed gel formulations.

S. NO	FORMULATION	*E. coli*	*P. aeruginosa*	*S. aureus*	*B. cereus*
		Zone of inhibition (mm)			
1.	F1	10.0 ± 0.6	9.0 ± 0.4	15.0 ± 0.5	14.0 ± 0.7
2.	F2	16.0 ± 0.8	14.0 ± 0.6	21.0 ± 0.9	17.0 ± 0.5
3.	F3	14.0 ± 0.7	11.0 ± 0.5	19.0 ± 0.6	15.0 ± 0.4
4.	F4	11.0 ± 0.5	9.0 ± 0.3	13.0 ± 0.5	10.0 ± 0.6
5.	F5	13.0 ± 0.6	12.0 ± 0.6	17.0 ± 0.4	13.0 ± 0.3
6.	F6	10.0 ± 0.5	8.0 ± 0.4	12.0 ± 0.6	7.0 ± 0.5
7.	Control	2.0 ± 0.2	1.0 ± 0.1	NA	NA
8.	Positive Control	10.0 ± 0.3	12.0 ± 0.5	8.0 ± 0.4	6.0 ± 0.3

NA- No measurable zone observed

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Author Contributions

First Author: Conceptualization, Data Curation, Formal Analysis, Project Administration, Supervision, Writing -original draft, Writing -review and editing. Second author: Data Curation, Formal Analysis, Investigation, Methodology, Resources, Writing -review and editing. Third author: Supervision, Project Administration and Writing -review and editing.

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