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ORIGINAL ARTICLE

Preformulation Study of *Kigelia africana* Fruit Ethanolic Extract as Topical Preparations

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Abstract

Background: **Preformulation studies have a significant role in anticipating formulation problems and identifying logical paths in dosage form technology.**

Aim: **This study aimed to evaluate the preformulation criteria of the aquatic ethanol extract of *Kigelia africana* fruit as topical antibacterial therapy.**

Methods: **The preformulation parameters of the extract were evaluated by testing its organoleptic characteristics, melting point, pH, spectroscopic assay, stability, solubility, and partition coefficient.**

Results: **The study demonstrated that the extract possessed satisfactory organoleptic properties, a melting point of 195.3−198.0 °C, a pH of 6.26, chemical stability under acidic conditions, photostability, higher solubility in basic conditions and in the presence of cosolvents, and a partition coefficient of 9.98.**

Conclusion: **The present study concludes that the aquatic ethanol extract of *K. africana* fruit is a suitable extract for formulation as a topical preparation.**

Keywords: Preformulation, *Kigelia africana*, Partition coefficient, Stability, Solubility, Topical preparations

Introduction

A preformulation study is defined as an investigation of the physical and chemical properties of a drug substance alone and when combined with an excipient (Acharya et al., 2018). It has a significant role in anticipating formulation problems and identifying logical paths in dosage form technology (Sigfridsson et al., 2017). The objective of the preformulation study is to develop an elegant, stable, effective, and safe dosage form by establishing a kinetic rate profile, compatibility with the other ingredients, and establishing the physico−chemical parameters of new drug substances (Verma & Mishra, 2016). *Kigelia africana* Lam (Benth) belongs to the family Bignoniaceae, commonly known as the sausage tree, and has a wide distribution in Africa, America, India, and Australia (Nabatanzi et al., 2020). *K. africana* is of medicinal value in most parts of Africa; the fruits are collected and traded locally in marketplaces as local medicine. Commercial value is attributable to industrially produced pharmaceutical products, for which fruits are harvested from naturally occurring trees. The fruits are also used in Africa to treat other infectious diseases including leprosy, impetigo, dermal complaints and infections such as whitlows, cysts, acne, and boils (Dossou-Yovo et al., 2022). To compose this herb into a pharmaceutically useful dosage form, the present study aimed to investigate the preformulation criteria to ensure stable drug products of *K. africana* fruits as an antibacterial topical therapy.

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Materials and methodology

Chemicals

Hydrochloric acid was sourced from S D FINE (India). Hydrogen peroxide was supplied by Bell Sons and Co. (England). N-octanol was obtained from ROMIL-SA (Germany). Propylene glycol was obtained from S.D. Fine-Chem (India). Polyethylene and glycol 400 were supplied by CDH (India). Additionally, Mueller-Hinton agar was provided by Scharlu (Spain).

Plant material

The *K. africana* fruit was collected, identified, and authenticated at the National Research Center, Medicinal and Aromatic Plant Institute, Khartoum, Sudan.

Preparation of extract

The extract was prepared by macerating 100 g of the dried *K. africana* fruit in 500 mL of ethanol at room temperature for 7 days. After the maceration period, the solvent was evaporated under reduced pressure using a rotary evaporator, following the procedure described by (Maqlam et al., 2019).

Preformulation tests

Organoleptic evaluation

The extract was evaluated for its color, odor, texture, and physical nature by direct observation.

Spectroscopic assay

The standard calibration curve of the extract was designed for quantitative analysis of the extract using a UV/Visible spectrophotometer (JENWAY – UK) as described by (Oshomoh et al., 2022).

Determination of λ_{max}

A solution of 0.1 mg/ml of the extract was prepared, and 2 ml of the solution was filled in a quartz cuvette, the UV/visible spectrophotometer was turned on, and the extract was scanned between 200 and 800 nm for λ_{max} determination. The mean of three readings was determined.

Standard calibration curve

A stock solution of 1 mg/ml of the extract was prepared and diluted to the following concentrations: 0.1 mg/ml, 0.08 mg/ml, 0.06 mg/ml, 0.04 mg/ml, and 0.02 mg/ml. Each dilution was placed in a quartz cuvette and the absorbance of each dilution was recorded at the determined λ_{max}, as triplicate, and the standard calibration curve was designed.

Melting range

A trace amount of the extract was put in a capillary tube 10 cm in length, sealed at one end, and dipped in a gradually heated electro-thermal thermometer (JENWAY-UK) to record the temperature (°C) at which the extract started melting and the temperature at which the extract completely melted (Alwan & Ibrahim, 2021).

pH measurement

One gram of the extract was dissolved in 100 ml of distilled water to give a concentration of 10 mg/ml. The electrode of the calibrated pH meter (JENWAY-UK) was immersed in the extract solution to obtain the pH of the extract (Kamtekar et al., 2014). This test was performed in triplicate.

Stability study

The stability was studied for hydrolysis, oxidation, and photolysis, as described by (Dos Santos et al., 2023). The extract was subjected to a chemical stability study using forced conditions stability study for six months according to the International Conference on Harmonization (ICH) guidelines (Rignall, 2017). The stability indicating method (SIM) was the biological assay of the extract by determination of the antibacterial activity of the tested extract against *Staphylococcus aureus*, the degraded extract will show decreasing antibacterial activity (Dafale et al., 2016).

Standard calibration curve

Serial dilutions of the extract were prepared in concentrations of 25 mg/ml, 50 mg/ml, 75 mg/ml, and 100 mg/ml. The Mean Diameter of the Inhibition Zone (MDIZ), as duplicate, was determined for each concentration against *S. aureus* using Mueller-Hinton Agar (MHA) as culture media. The standard calibration curve was designed which consists of extract concentrations (mg/ml) as the independent variable versus MDIZ (mm) as the dependent variable.

Hydrolysis

The stability of the extract was studied in aqueous media at pH: 4, 5, 6, 7, and 8, at temperatures 25 °C, 40 °C, and 60 °C. These pH values are the possible pH values of formulations and skin. One ml vial was filled with 10% w/v solution of extract, HCl, and phosphate buffer were added for adjustment of pH, and the filled vials were stored for 7 days. Before the removal of samples for analysis, sodium bicarbonate was added

for sample solutions of an acidic nature for neutralization of solution, and the HCl was added for neutralization of sample solutions of a basic nature.

Oxidation

One ml vials were filled with a 10% w/v of extract. A 3% H_2O_2 was added as the oxidizing agent, where the pH was adjusted to a pH 5 as the pH of the most stable solution from the hydrolysis experiment. The vials were then stored at 25 °C, 40 °C, and 60 °C in ovens for 7 days. Before the removal of samples for biological assay, sodium sulfite was added for each extract for a reaction with hydrogen peroxide to inhibit its antibacterial activity.

Photolysis

One ml vials were filled with 10% w/v of each extract at pH = 5 and placed in a UV lamp (BTL–India) for 7 days, while the other 1 ml vials were filled with 10% w/v of each extract at pH 5 and placed in fluorescent light. An aliquot of 0.1 ml of samples was removed for the determination of antibacterial activity against *S. aureus* by determination of MDIZ and substitution in a regression equation for determination of degradation percent.

Solubility

The solubility of the extract was determined in different solvent systems according to (Aulton & Taylor, 2013), in which pH and co-solvency approaches were modulated. The excess amount of extract was added separately with increasing amounts gradually to vials containing the following systems: Distilled water pH = 7.2, diluted HCl pH = 4, diluted HCl pH = 5, diluted HCl pH = 6, phosphate buffer pH = 8, phosphate buffer pH = 9, propylene glycol, polyethylene glycol 400, glycerol, water: propylene glycol 3:1, water: polyethylene glycol 400 3:1, and water:glycerol 3:1. These systems were shaken continuously for 24 h at magnetic stirrer with adjustment of temperature at 25 °C and 37 °C separately. After 24 h, the vials were let for equilibrium and the vials with turbidity or precipitate were separated from those of completely dissolved systems using a magnifying glass, a sample of each grade of solutions was filtered using a pipette supported with a filter paper. The vials remained on a magnetic stirrer at 25 °C and 37 °C with pipetting; the pipette solution was diluted, transformed to a quartz cuvette as soon as possible, and analyzed for absorbance using UV⁄visible spectrophotometer for determination of concentration. The solubility was expressed as intrinsic solubility in mg/ml^{-1}, and as descriptive solubility, as described by United States Pharmacopoeia and European Pharmacopoeia.

Partition coefficient

The partition coefficient was determined using the shake flask method, as described by (Andrés et al., 2015). The specific amount of extract was added to buffered purified water (pH = 7.4) as an aqueous phase (C_w initial) to obtain aqueous solutions of the following concentration: 1 mg/ml, 2 mg/ml, and 3 mg/ml. An equal volume of n-octanol as an oily phase was added to the aqueous phase and mixed into the three separate flasks each of 500 ml volume, the systems were shaken continuously at 25 °C for 24 h and finally left to separate for 1 h. One ml sample from the aqueous phase was removed for analysis by UV/visible spectrophotometer for measurement of absorbance and the concentration (C_w final) was determined from the regression equation of the standard calibration curve of each extract. The partition coefficient was determined from the following equation:

$$P = \frac{C_O}{C_W}$$

- **P:** Partition coefficient
- **C_o:** Concentration of extract in the oily phase
- **C_w:** Concentration of extract in the aqueous phase = C_w initial − C_w final. C_w initial refers to the concentration of extract in the aqueous phase before the study (known concentration), and C_w final refers to the concentration of extract in the aqueous phase after the study (from regression equation).

Statistical analysis

Data were expressed as mean ± standard deviation (SD), and were analyzed by one-way analysis of variance (ANOVA) followed by Tukey HSD test for multiple comparisons.

Results

Organoleptic properties of K. africana *fruit extract*

- *Color:* Brownish black
- *Odor:* Not distinctive
- *Texture:* Smooth
- *Physical nature:* Gummy

Spectrophotometric assay of K. africana *fruit extract*

The *K. africana* fruit extract exhibited a maximum absorbance (λ_{max}) at 236 nm, as determined through spectrophotometric analysis. A standard calibration

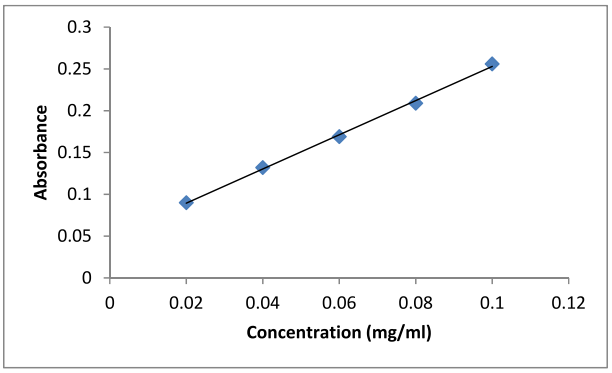

Fig. 1. Standard calibration curve of extract of K. africana *fruits.*

curve was generated, showing a linear relationship between the absorbance and extract concentration (mg/ml), as shown in Fig. 1.

Melting point and pH of K. africana *fruit extract*

The melting range is 195.3–198.0 (°C). The melting point indicates that the extract remains solid at ambient temperatures, which is useful for stability in formulations, especially in warm climates. Whereas, the pH is 6.26 ± 0.01 (Mean ± SD), where the slightly acidic pH suggests that the extract is close to neutral, which could promote compatibility in various topical applications without requiring significant pH adjustments.

Stability of K. africana *fruit extract*

The stability results of *K. africana* fruit extract under forced hydrolysis, oxidation, and photolysis conditions are shown in Table 1. Stability was evaluated based on the mean diameter of the inhibition zone (MDIZ), concentration, and percentage content across different pH levels, temperatures, and exposure to light.

Solubility of K. africana *fruit extract*

The intrinsic and descriptive solubility of the extract in different solvent systems are displayed in Table 2.

Partition coefficient of K. africana *fruit extract*

The partition coefficient of the *K. africana* fruit extract, measured between octanol and water phases using the shake flask method, was 9.98 ± 0.5, with a log *P* value of 0.99.

Discussion

The brownish-black color of the extract provides usually brown colors final products of different grades and the non-distinctive odor of the extract ensures the non-distinctive odor of the formulations which ensures the needless addition of a flavoring agent. Its smooth texture due to its gummy nature

Table 1. Stability of K. africana *fruit extract against hydrolysis, oxidation, and photolysis using forced conditions.*

Test	Storage condition		Content %		
	pH	Temperature (°C)	MDIZ[a] (mm)	Concentration (mg/ml)	Content (%)
Hydrolysis	4	25	26.0 ± 1.4	92.6 ± 0.1	92.6 ± 0.5
		40	26.0 ± 0.0	92.6 ± 0.0	92.6 ± 1.2
		60	25.0 ± 1.4	89.3 ± 0.9	89.3 ± 0.9
	5	25	28.0 ± 2.1	99.2 ± 0.0	99.2 ± 0.0
		40	28.0 ± 1.4	99.2 ± 0.2	99.2 ± 0.1
		60	27.0 ± 1.4	95.8 ± 1.2	95.8 ± 0.6
	6	25	28.5 ± 0.7	100.8 ± 0.0	100.8 ± 0.0
		40	28.0 ± 1.4	99.2 ± 0.5	99.2 ± 0.1
		60	27.0 ± 2.1	95.8 ± 0.6	95.8 ± 0.8
	7	25	27.0 ± 1.4	95.8 ± 0.4	95.8 ± 1.0
		40	27.5 ± 0.7	97.5 ± 0.1	97.5 ± 1.1
		60	25.0 ± 1.4	89.3 ± 1.2	89.3 ± 1.6
	8	25	23.0 ± 1.4	82.7 ± 1.0	82.7 ± 1.5
		40	21.0 ± 0.0	76.0 ± 0.5	76.0 ± 0.9
		60	20.5 ± 0.7	74.4 ± 0.9	74.4 ± 0.4
Oxidation	5	25	27.0 ± 2.1	95.8 ± 0.1	95.8 ± 0.8
		40	26.0 ± 0.0	92.5 ± 1.4	92.5 ± 0.2
		60	24.5 ± 0.7	87.6 ± 1.2	87.6 ± 1.5
Photolysis	UV (UV lamb)		27.0 ± 1.4	95.8 ± 0.0	95.8 ± 0.0
	Fluorescent light		26.0 ± 2.1	92.5 ± 0.2	92.5 ± 0.6

The results are expressed as the mean ± SD (n = 3).
[a] MDIZ stands for Mean diameter of inhibition zone.

Table 2. Solubility of K. africana *fruit extract in different solvent systems at 25 °C and 37 °C.*

Solvent System	Temperature			
	25 °C		37 °C	
	Solubility (mg/ml)	Descriptive solubility	Solubility (mg/ml)	Descriptive solubility
Distilled water pH = 7.2	4.81 ± 0.01	Slightly soluble	7.01 ± 0.08	Slightly soluble
HCl solution pH = 4	0.10 ± 0.20	Very slightly soluble	1.26 ± 0.12	Slightly soluble
HCl solution pH = 5	2.96 ± 0.40	Slightly soluble	3.52 ± 0.63	Slightly soluble
HCl solution pH = 6	4.38 ± 0.02	Slightly soluble	6.78 ± 0.28	Slightly soluble
Phosphate buffer solution pH = 8	17.65 ± 0.15	Sparingly soluble	21.60 ± 0.05	Sparingly soluble
Phosphate buffer solution pH = 9	30.13 ± 0.23	Sparingly soluble	37.32 ± 0.02	Soluble
Propylene glycol	89.17 ± 0.01	Soluble	95.44 ± 0.28	Soluble
PEG 400	86.56 ± 0.28	Soluble	89.70 ± 0.75	Soluble
Glycerol	63.68 ± 0.06	Soluble	86.00 ± 0.39	Soluble
Water: propylene glycol	139.18 ± 0.68	Freely soluble	163.11 ± 0.85	Freely soluble
Water: PEG 400	112.00 ± 0.08	Freely soluble	129.32 ± 0.02	Freely soluble
Water: Glycerol	131.13 ± 0.04	Freely soluble	158.90 ± 0.05	Freely soluble

The results are expressed as the mean ± SD (n = 3).

enhances the texture of the final product (Ramadhanty et al., 2023). The melting range of the extract indicates its solid state at ambient temperature and resistance to liquefaction in hot climate conditions. The melting points depend on intermolecular forces between molecules of extract, where the nature of phenolic compounds may be attributed to this melting point (Lama-Muñoz & Contreras, 2022). The pH of a 1% solution of extract indicates its acidic nature. It's usually the pH of weak acids. The major components of the extract were the phenolic compounds, which contributed to the acidic nature of the extract as described by (Kumar & Goel, 2019). It would not change the pH of the final product extremely, so that no buffer would be added, and further, physiological compatibility between the extract final product and the skin would be attained. The extract showed stability in acidic media and instability with increasing pH, as shown in Table (1). This indicates the acidic nature of the extract because weak acids are less stable in basic conditions. The ionization of weak acids increases in basic conditions and ionized charged molecules are unstable in these conditions, as detailed by (Aulton & Taylor, 2013). This is valuable because the pH of the final product should be less than 7 as this was the pH at which degradation was significant and the maximum stability was at pH = 5 because this was the pH of maximum unionized part concentration. The extract was stable against oxidation, this may be due to the antioxidant activity of the extract of phenolic compounds as stated by (Volf et al., 2014), because of their hydrogen bonding ability and aromaticity, phenolic compounds can frequently act as free radicals scavengers, forming aryloxy radicals. The stabilization of these radicals by other functional groups enhances the antioxidant activity. There are several studies concerning topically applied antioxidant products for this purpose (Saija et al., 2000), and for these attributes, no antioxidant should be added. The extract was photostable and hence no effect of light regarding the storage conditions of the extract or either final product besides the package of the final product in aluminum collapsible tubes which protect the product from the effect of light.

The extract was slightly soluble in distilled water and in acidic conditions, the solubility was decreased due to the acidic nature of the extract as the solubility of weak acids usually decreases in acidic media for increasing unionized part concentration which usually means less water solubility according to ionization equilibrium rule and vice versa as explained by (Amiji & Sandmann, 2014; Honmane, 2017). The extract showed higher solubility in polyhydric alcohols (polyols) solvents as referred to in Table (2). The extraction solvent ethanol:water usually dissolves rapidly with alcohol:water solvent system due to its resemblance in chemical nature and hence intermolecular forces between the molecules solutes and solvent system will be formed (Amiji & Sandmann, 2014). So, the addition of propylene glycol as cosolvent to aqueous phases of our products will increase the solubility of extract prompting finally the release of extract from the vehicle. Propylene glycol is used widely in skin topical formulations as a cosolvent, humectant, and penetration enhancer (Williams, 2007; Yu & Goh, 2024).

Conclusion

The study confirms that the ethanolic extract of *K. africana* fruit is suitable for formulation as a topical preparation. The results demonstrated good stability under acidic conditions, with high solubility in

basic environments and cosolvents, enhancing its potential for pharmaceutical applications.

Author's contribution

All authors equally contributed to the design and implementation of the study.

Ethics information

This study involved only in vitro bacterial experiments and did not require approval from an Institutional Review Board (IRB) or Animal Ethics Committee. No human or animal subjects were used in this research. The authors declare no conflicts of interest.

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Conflicts of interest

The author declares no conflicts of interest.

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