Review Article
Pharmaceutical Properties and Applications of a Natural Polymer from *Grewia mollis*

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The use of naturally occurring biocompatible materials has been the focus of recent research activity in the design of dosage forms for immediate and controlled release formulations. Grewia gum is an intracellular gum obtained by extraction from the inner stem bark of the shrub *Grewia mollis* (Malvaceae). It grows abundantly (wild or cultivated) in the middle belt region of Nigeria, and the mucilage has been used by indigenes of this belt as thickener in soups. Grewia gum has been investigated for potential applications in pharmaceutical dosage forms. The industrial extrapolation of the applications of the gum has, however, been slowed by the limited structural, toxicological, and stability data available on the gum. This paper highlights ethnobotanical uses of *G. mollis* shrub and discusses the structural features, functional properties, and applications of grewia gum with emphasis on its pharmaceutical potentials.

1. Introduction

Plant materials are playing increasing role as alternatives to chemical food additives and synthetic pharmaceutical excipients. Natural polysaccharide gums swell to form highly viscous solutions or dispersions in aqueous media. They have the advantage of biocompatibility, low cost, and relative abundance [1] compared to their synthetic counterparts. They are widely used in the pharmaceutical industry as polymers in various drug delivery systems [2–7].

Grewia polysaccharide gum is a natural resource that could be used as an excipient in the pharmaceutical industry in Nigeria to reduce the costs of pharmaceutical products. It may provide a suitable alternative to the synthetic counterparts which are expensive and mostly imported. It is obtained by extraction (maceration in cold or hot water) of the inner stem bark of the edible plant *G. mollis*, Juss (Malvaceae). In Nigeria, *G. mollis* from which the gum is extracted grows abundantly (wild or cultivated) in the middle belt region of the country where it is used as thickener in local delicacies.

This review delineates the ethnobotanical uses, physico-chemical properties, structural properties, and the potential applications of the gum in drug delivery systems.

2. *Grewia mollis* Plant

*G. mollis* belongs to the flowering plant genus, *Grewia*. It was formerly placed in the family Tiliaceae or Sparrmanniaceae. Today most authors place the genus in the mallow family Malvaceae.

2.1. Botany. The plant has been described [8, 9] as a shrub or small tree growing to attain a height of 10.5 m with young branches densely stellate-pubescent. The young branches turn dark grey to black or reddish brown when older.

The leaves of the plant are elliptic to elliptic-oblong, usually between 2.0 and 14.5 cm long and 0.7 and 5.5 cm wide. They are acute to slightly acuminate at the apex, broadly rounded or obliquely truncate at the base. The leaf margins are coarsely and sharply serrate, more or less glabrous to sparsely minutely stellate-pubescent above, but densely and finely greyish to brownish white-pubescent beneath [9].

The flowers are yellow and bisexual; sepals 6–10 mm long; petals obviate to oblong, 4–6 mm long, ±2 mm wide, and sometimes notched at the apex. The ovary is 1.5–2 mm long and densely hairy [9].
Table 1: Ethnomedicinal uses of G. mollis plant.

<table>
<thead>
<tr>
<th>Use</th>
<th>Plant part</th>
<th>Preparation</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound healing</td>
<td>Bark, leaves</td>
<td>Mucilages are applied to ulcers, cuts, sores, and snake bites</td>
<td>[9, 13]</td>
</tr>
<tr>
<td>Cough</td>
<td>Bark, roots</td>
<td>Decoction</td>
<td>[9, 13]</td>
</tr>
<tr>
<td>Fever</td>
<td>Bark, leaves, and fruit</td>
<td>Extract of bark and/or leaves. Fruits are also eaten for this purpose</td>
<td>[9, 13]</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Stem bark</td>
<td>Decoction</td>
<td>[9, 24]</td>
</tr>
<tr>
<td>Child birth Pain</td>
<td>Stem bark, leaves</td>
<td>Maceration, decoction</td>
<td>[9, 13]</td>
</tr>
<tr>
<td>Colic</td>
<td>Bark, leaves</td>
<td>Infusion</td>
<td>[9]</td>
</tr>
<tr>
<td>Constipation</td>
<td>Bark</td>
<td>Mucilage</td>
<td>[9]</td>
</tr>
<tr>
<td>Rickets</td>
<td>Leaves</td>
<td>Decoction</td>
<td>[9]</td>
</tr>
<tr>
<td>Palpitation</td>
<td>Roots, leaves</td>
<td>Decoction</td>
<td>[9]</td>
</tr>
<tr>
<td>Sore eyes</td>
<td>Root shavings</td>
<td>Sap squeezed out and applied under the eyelid</td>
<td>[9]</td>
</tr>
<tr>
<td>Rheumatism</td>
<td>Roots</td>
<td>Paste</td>
<td>[9, 13]</td>
</tr>
<tr>
<td>Anal prolapse</td>
<td>Bark</td>
<td>Pounded and dissolved in water</td>
<td>[9, 24]</td>
</tr>
</tbody>
</table>

3.2. Vegetables and Fruits. The flowers, buds, and young shoots are added to soups and sauces as garnishing while, in Sudan, the young leaves are cooked and eaten as vegetables. The fruit is eaten raw or boiled [9].

3.3. Ethnomedicinal Uses. Several ethnomedicinal uses of the infusion, decoction, maceration, or mucilage from the leaves, roots, or stem bark of G. mollis have been documented. These ethnomedicinal uses are described in Table 1.

4. Biological Evaluation and Chemical Constituents of G. mollis

Several scientists have investigated the histopathological and toxicological effects of extracts of G. mollis on laboratory animals.

Onwuliri et al. [14] conducted toxicological and histopathological studies in rats using the ethanolic extract of the stem bark of G. mollis. Tannins, saponins, flavonoids, glycosides, balsam, phenols, terpenes, and steroids were isolated from the stem bark, but alkaloids were absent. The extract exhibited toxic properties at the lethal dose (LD$_{50}$) of 1500 mg/kg body weight. The convoluted tubules of the kidney but no structural effects on the liver and heart were observed suggesting that the extract may be safe in humans but should be used with caution on patients with renal failure.

Studies by Obidah et al. [12] on the toxic effects of the stem bark of G. mollis showed that the addition of the pulverized stem bark to the normal diet of male Wister rats at concentrations of 0, 1, 5, and 10% given to them as feed for 4 weeks, resulted in no deaths, and remarkable changes in appearance were not observed in the treated animals. However, rats fed with 10% dietary level showed significant ($P < 0.05$) increases in serum transaminases activities which was accompanied by decreased food intake. There was no observed effect on serum alkaline phosphatase activity, urea, creatinine, triglycerides, cholesterol, glucose concentrations, and body and organ weights in their study. These workers concluded that dietary exposure of rats to G. mollis stem bark powder at high concentrations (10%) may cause some adverse effects, especially liver injury.
It may be argued however that gum extracted from the stem bark of *G. mollis* when used as excipient is incorporated into formulations in smaller proportions usually lower than the 10% proportion added to the feed of the animals in the foregoing study. Consequently, it may be expected that the low use level of *G. mollis* gum as excipient in formulations should not cause any adverse effects in humans.

Asuku et al. [15] evaluated the methanolic extract of *G. mollis* leaves for its antioxidant and hepatoprotective properties by an *in vivo* procedure. They reported significant (*P* < 0.05) hepatoprotective potential evidenced by the lowering of serum levels of bilirubin, aspartate aminotransferase, and alanine aminotransferase and decreasing of malondialdehyde levels in rats pretreated or posttreated with carbon tetrachloride (CCl₄). They concluded that *G. mollis* leaves contain potent antioxidant compounds that could offer protection against hepatotoxicity and ameliorate preexisting liver damage and oxidative stress conditions.

Saleem et al. [16] assessed the nutritive value of the leaves and fruits of three *grewia* species under semi-arid environment, and the results of the study indicated that the three species could be introduced as a source of fodder in animal production farms and silvopastoral systems.

### 4.1. Compounds Isolated from *G. mollis*

Al-Youssef et al., [17] evaluated the methanolic extract of the aerial part of *G. mollis* and reported isolation of a number of phytochemical constituents such as flavonoids (luteolin and 7-(1-O-β-D-galacturonide)-4′-(1-O-β-glucopyranosyl)-3′,5,7-tetrahydroxyflavone), triterpenoids (7β-hydroxy-23-enedo lexojessic acid and 7β-hydroxy-23-deoxojessic acid), and steroids (β-sitosterol and β-sitosterol-3-O-glucoside). The molecular structures of these isolates are shown in Figure 2.

Rosler et al. [18] earlier reported the isolation of 6-methoxyharmane (Figure 2(g)), a Harman alkaloid from *G. mollis*. Harman alkaloids belong to the class of β-carbolines. They bind strongly to benzodiazepine receptors in the brain to induce inverse agonist effects to benzodiazepines such as convulsive, anxiogenic, and memory enhancing effects [19–21].

Efiom and Oku [22], working on the *n*-hexane fraction of *G. mollis* root extract collected in Niger State, Nigeria, isolated two triterpene compounds, lup-20-en-3-ol and 1,3-hexyloxacyclotridec-10-en-2-one.

### 4.2. Phytochemical Screening, Antibacterial and Anti-Inflammatory Properties

Shagal et al. [23] reported the presence of saponins and phenolic compounds in the ethanolic fraction of *G. mollis* leaves while glycosides were additionally present in the ethanolic stem bark extracts. Tannins, volatile oils, and flavonoids were also observed in the ethanolic root extracts.

Antibacterial studies on the ethanolic leaf and root extracts were reported to exhibit inhibitory activity against *Staphylococcus aureus* and *Escherichia coli* while the stem bark extract exhibited activity against *S. aureus* and *Salmonella typhi*. The aqueous root extracts showed no inhibition against the same organisms except for the aqueous leaf extract which showed some inhibitory activity against *Streptococcus* spp. and *E. coli*. The aqueous extract of the stem bark also exhibited inhibition against *S. typhi* which possibly justifies the use of the plant in the treatment against diarrhoea and dysentery.
Al-Youssef et al. [17] investigated the in vitro antibacterial activity of the aerial part of *G. mollis* collected in Akba-Al-Abar, Saudi Arabia, against various strains of bacteria such as *Staphylococcus epidermidis* (ATCC 9615), *Bacillus subtilis* (ATCC 1174), *S. aureus* (ATCC 25175), *Klebsiella pneumonia* (ATCC 33495), *Pseudomonas aeruginosa* (ATCC 12453), and *E. coli* (ATCC 10536). Moderate inhibitory activity was exhibited by the methanolic extract against *S. epidermidis*, *B. subtilis*, and *S. aureus* when compared with the standard antibiotics cloxacillin (5 mcg/disc), amoxicillin (10 mcg/disc), and ciprofloxacin (5 mcg/disc). The extract also showed inhibitory activity against oral cavity pathogen, *S. aureus*, at MIC value of 64 mcg/ml and 128 mcg/ml against methicillin resistant *S. aureus* (MRSA, ATCC 15187), respectively. The authors reported a time and concentration dependent killing by the methanolic extract of *G. mollis* against *S. aureus* (ATCC 25175).

The development of a new class of polyurethane nanofibers containing aqueous extract of aerial parts of *G. mollis* by one step electrospinning was reported by Musarat et al. [25] for its potential biomedical application as an antimicrobial fiber. They incorporated the aqueous extract into the polymer media in order to influence the morphology and size of the polyurethane nanofibers. Further testing of the extract loaded nanofibers was also observed to inhibit the growth of *E. coli* (ATCC 52922) and *S. aureus* (ATCC 29231).

Al-Youssef et al. [17] also investigated the anti-inflammatory activity of the same extract at 500 mg/kg which showed pronounced anti-inflammatory effect after two hours. Their findings provide preliminary evidence suggesting that fractions of *G. mollis* exhibit inhibitory effects in inflammatory process and support the use of this plant for the treatment of arthritis, dermatitis, and wounds in African and Saudi Arabian traditional medicine.

5. Grewia Polysaccharide Gum

Interest in grewia polysaccharide gum as a pharmaceutical excipient has been on for over a decade [26]. This growing interest is informed by the viscous property of the gum extract from the inner stem bark of the shrub *G. mollis* (ATCC 9615), and *Bacillus subtilis* (ATCC 12453), and *E. coli* (ATCC 10536). Moderate inhibitory activity was exhibited by the methanolic extract against *S. epidermidis*, *B. subtilis*, and *S. aureus* when compared with the standard antibiotics cloxacillin (5 mcg/disc), amoxicillin (10 mcg/disc), and ciprofloxacin (5 mcg/disc). The extract also showed inhibitory activity against oral cavity pathogen, *S. aureus*, at MIC value of 64 mcg/ml and 128 mcg/ml against methicillin resistant *S. aureus* (MRSA, ATCC 15187), respectively. The authors reported a time and concentration dependent killing by the methanolic extract of *G. mollis* against *S. aureus* (ATCC 25175).

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5.2. Some Physicochemical Properties of Grewia Gum. The gum contains traces of metals (Ca, K, Na, Mg, Zn, and Fe) and a viscosity-average-molecular weight of 316,000 [28]. Metals constitute about 6.1% of the gum, while proteins and lipids account for 1.24 and 0.021%, respectively. It has a high intrinsic viscosity with a swelling capacity greater than tragacanth and methylcellulose.

Grewia polysaccharide gum slowly hydrates and swells in water. The gum has aqueous solubility of about 0.2 mg/mL [29]. The low solubility of the gum was attributed to insoluble cell-wall materials making up a larger proportion of the gum. However, the presence of acetyl groups has been reported to account for the insolubility of certain gums in water [31]. Grewia polysaccharide gum has been shown from Fourier-transformed infrared (FTIR) spectroscopic studies to contain acetyl groups which may account for the low solubility of the gum in water [29]. Generally, water poorly soluble gums due to presence of acetyl groups are improved by deacetylation with dilute ammonia [31–33].

The rheological properties of the gum dispersion and the water vapour permeability of aqueous-based grewia gum films have been reported [27, 34]. The aqueous dispersions of the gum at different concentrations exhibited pseudoplastic flow behaviour. The viscosities of the gum dispersions decrease with increase in temperature. The effect of incorporation of electrolytes to dispersions of the gum was also investigated. The result showed a decrease in the viscosity of the gum brought about by electrolyte which is proportional to the concentration as well as the valence of the cation, and these findings have been confirmed by other workers [29].

5.3. Chemistry of Grewia Gum. Okafor [27] using paper chromatography reported that the primary structure of grewia polysaccharide gum may comprise of d-glucose, d-rhamnose and galacturonic acid. Nep and Conway [29, 35] determined the monosaccharide composition of the gum using gas chromatography. These workers reported that the primary structure of grewia gum may comprise five neutral sugars: d-rhamnose, d-arabinose, d-xylose, d-galactose, and d-glucose (Figure 3). The mean relative concentrations of these sugars in the polysaccharide were determined as glucose (67.14%), rhamnose (6.2%), xylose (2.72%), galactose (9.61%), and arabinose (12.71%).

The FTIR spectral analysis of the gum exhibited the typical bands and peak characteristics of polysaccharides [29] as shown in Figure 4. These authors attributed the broad band occurring at about 3425 cm⁻¹ to the presence of hydroxyl (–OH) groups while the peak obtained at about 2927 cm⁻¹ was attributed to stretching modes of the C–H bonds of methyl groups (–CH₃) of the rhamnose. Absorption bands around 1618 and 1420 cm⁻¹ were attributed to carboxylate groups of uronic residues of galacturonic acid while the region between 1500 and 1800 cm⁻¹ and absorption peaks at 1735 cm⁻¹ and 1256 cm⁻¹ were linked to the presence of carboxylic and acetyl groups, respectively. The absorption
band between 500 and 900 cm\(^{-1}\) may represent the fingerprint region for grewia polysaccharide gum.

The gum has also been characterized using other techniques such as scanning electron microscopy (SEM), gel permeation chromatography (GPC), differential scanning calorimetry (DSC), and thermogravimetric analysis of the extracted sample. Also, spectroscopic techniques such as X-ray photoelectron spectroscopy (XPS), solid-state nuclear magnetic resonance (NMR), and \(^1\)H and \(^{13}\)C NMR techniques [29] have been employed in the characterization of grewia gum. Based on findings from the various techniques, the gum has been described as a typically amorphous polysaccharide gum of high thermal stability with an average molecular weight of 5925 kDa expressed as the pullulan equivalent.

The effect of drying methods (air-drying, freeze-drying, and spray-drying) on the physicochemical properties of the gum has been investigated using the techniques outlined above [35]. Solid-state NMR results indicated that drying technique had little effect on the structure of the polysaccharide gum, but X-ray photoelectron spectroscopy (XPS) showed that surface chemistry of the gum varied with drying methods. Thermogravimetric analyses showed that oxidation onset varied according to the drying method. The workers concluded that, for industrial extrapolation, air-drying of the gum may be preferable to spray-drying and freeze-drying when relative cost, product stability, and powder flow are the priority, in tablet formulation, for instance.

6. Pharmaceutical Values of Grewia Polysaccharide Gum

6.1. Preformulation Studies. The assessment of possible interactions between a drug and different excipients used in formulation usually precedes large scale development trials of solid dosage forms [36, 37]. Physical and chemical interactions between excipients and active pharmaceutical ingredients (API) are common place [38] and necessitate the screening of novel excipients for possible incompatibilities. In view of the suitability of grewia polysaccharide gum as formulation excipient in solid or liquid dosage forms, studies on the potential interaction or incompatibility of the gum with pharmaceutical actives and/or excipients used in solid dosage formulation are imperative.

Nep and Conway [39] investigated potential interactions between grewia gum and cimetidine, ibuprofen, and some standard excipients used in the formulation of tablets (Figure 5). The thermal and molecular behaviours of mixtures of grewia gum with cimetidine, ibuprofen, and the standard excipients (lactose monohydrate, magnesium stearate, colloidal silicone dioxide, and microcrystalline cellulose) were analyzed using differential scanning calorimetry and FT-IR spectroscopy to assess potential interactions. The results obtained indicated that grewia gum is an inert natural polymer which can be used alone or in combination with other excipients in the formulation of pharmaceutical dosage forms.

6.2. Pharmaceutical Applications. Investigations into the pharmaceutical application of gum from \textit{G. mollis} were first reported in the early 2000s [27, 28, 34, 40, 41]. The gum was reported to possess excellent binding property in sodium salicylate tablets (Okafor and Chukwu [40]). It was found to be as effective as gelatin when employed as a binder in concentrations of 2–6\% w/w. At the same concentration, the gum was more effective as a binder than maize starch or acacia gum.

Audu-Peter and Gokum [42] found that the method of incorporating the gum into tablet formulation had effect...
Grewia gum has been investigated as a sustained release polymer matrix in ibuprofen [44]. It was used at a concentration of 16%, 32%, or 48% to formulate tablets of ibuprofen. This was compared with similar formulations prepared using hydroxypropyl methylcellulose (HPMC), guar gum, or ethyl cellulose as the polymer matrix. The results indicated that grewia gum at these concentrations was capable of sustaining the release of ibuprofen tablets up to 24 hours (Figure 6). Similarly, these scientists demonstrated the potential of grewia gum to sustain the release of a water-soluble drug in tablet formulations [45]. Tablets of cimetidine containing 40% of grewia gum were prepared by direct compression.

Similar formulations containing HPMC, gum Arabic, carboxymethylcellulose, or ethyl cellulose were prepared for comparison. The results indicated that grewia gum was superior to hydrophilic matrices of HPMC, carboxymethylcellulose, and gum Arabic in sustaining the release of cimetidine from tablets. In both instances, the workers concluded that grewia gum may be a useful excipient when used alone or in combination with other polymers to modify the release of soluble drugs or poorly soluble drugs from polymeric matrices.

Grewia gum fractions obtained by centrifugation at 4500 rpm for 30 minutes with average molecular weights between 230 and 235 kDa have been shown to demonstrate improved aqueous solubility that was useful in delivering more solids to the substrate when used as a film coating agent [26, 30].

Grewia gum has also been evaluated as a mucoadhesive in tablets [46–48]. Nep and Okafor [47] showed that the gum compared favourably with tragacanth when used as bioadhesive in tablet formulation. Nep and Conway [48] compared the mucoadhesive performance of compacts or gels of grewia polysaccharide gum with those of guar gum, carboxymethylcellulose, hydroxypropyl methylcellulose, and carbopol 971P. A software-controlled penetrometer, TA.XTPlus texture analyzer (Stable Microsystems, UK) was used to measure the detachment force of the compacts while the polymer gels were evaluated for hardness, stickiness, work of cohesion, and work of adhesion. The results showed that grewia gels had a significantly greater work of adhesion than carboxymethylcellulose gels (P < 0.05) and HPMC gels (P < 0.001). The mucoadhesive performance of grewia compacts was comparable to those of HPMC and carbopol 971P compacts (P > 0.05). It was concluded that grewia polysaccharide gum should be suitable for the formulation of retentive drug delivery devices.

The application of the gum as a suspending agent in paediatric formulations has been reported [49–51]. The suspending ability of air-dried or freeze-dried grewia gum in ibuprofen suspension was compared with similar suspension formulations containing xanthan gum, sodium carboxymethylcellulose, or acacia gum as suspending agents [49]. The stability of the ibuprofen suspension formulations was assessed using parameters such as appearance, pourability, viscosity, rheology, sedimentation volume and redispersibility. Other evaluation parameters used include degree of flocculation, zeta potential, and microbial load. The result from the study indicated that air-dried or freeze-dried grewia gum may provide a suitable alternative as suspending agent in paediatric suspension formulations.

7. Conclusion

Grewia gum is a natural resource whose potential pharmaceutical values have been established. Our literature survey revealed that, pharmaceutically, grewia gum has been well investigated for its application as binder, disintegrant or mucoadhesive in solid dosage forms and as stabilizer or suspending agent in liquid formulations. However, the scientific research on grewia gum is yet to be translated into industrial applications due to the absence of detailed physical and chemical characterization, stability data, and scientifically validated bioactive properties. Although the use of grewia gum as thickener in local delicacies spans generations, it may be necessary to reconcile the ethnomedicinal use of extract of the aerial parts of the plant with the absolute requirement that excipients are pharmacologically inert. Detailed scientific investigations that will fill in these details will not only help in furthering the scientific understanding of grewia gum, but importantly it will assist in realizing its commercial...
potential as pharmaceutical excipient. Furthermore, grewia gum should be explored in design and development of other drug carriers such as micro- and nanomaterials, membranes, capsules, and hot-melt extruded carriers and in wound healing applications. Grewia gum holds promise as an excipient to be explored for the unmet needs in drug delivery.

Conflict of Interests
The authors certify that there is no conflict of interests with any financial organization regarding the material discussed in the paper.

References


