HERBAL FORMULATION AND PHARMACEUTICS

A Review on the Evaluation of Plumbago zeylanica Topical Preparations

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Published November 2026

Abstract

Plumbago zeylanica L. (Chitrak) has been used within traditional medicine for many years. Due to it being reported to have antimicrobial, anti-inflammatory, antioxidant and wound-healing effects there has been an interest in creating topical products from this plant. *Plumbago zeylanica* contains various phytochemicals such as naphthoquinones, flavonoids, tannins, terpenoids and sterols. However, plumbagin in particular has attracted interest due to its biological activity. However, even though promising results were found using extracts of the plant or isolated compounds, this does not guarantee that the final product will be safe and effective. This narrative review will discuss the scientific reasoning behind creating a topical product from *Plumbago zeylanica*. This includes looking at aspects such as identification, standardisation, appearance, pH, rheology, homogeneity, release, skin distribution, biological activity, safety and stability. Whilst there is evidence to suggest further investigation could be done, especially regarding wound healing, the evidence is mainly pre-clinical. Future development should focus on creating a reproducible formulation, appropriate controls and ensuring that the biological activity relates to skin tolerance. Clinical trials will be needed before making definite claims about the therapeutic effect.

Keywords: Plumbago zeylanica; Chitrak; plumbagin; topical formulation; herbal formulation; wound healing; skin safety

1 Introduction

Plumbago zeylanica is a medicinal plant belonging to the Plumbaginaceae family. It is well known as Chitrak and has been used within traditional medicines for various conditions. Due to its reported external uses and experimental findings showing it has antimicrobial, anti-inflammatory and wound-healing activity there has been interest in creating a topical formulation [1].

Creating a useful topical formulation means that you need to ensure the formulation contains a consistent amount of the chosen compounds, it is stable and the formulation will have appropriate spreadability when applied [3, 4].

It is important to consider the safety. Plumbagin is one of the main bioactive compounds present in the plant. This means that depending on the concentration and experimental conditions you may get different effects. If you create a formulation that will improve delivery it may also affect the risk of local toxicity. The goal should be to create an effective formulation that will have useful biological activity without causing unacceptable damage to the skin [2].

This review will bring together the pharmacological reasoning for creating a topical formulation and what needs to be considered when evaluating the final formulation.

2 Scope of the review

This article is a narrative review based mainly on the botanic and pharmacological information provided by Shukla et al. Other information has been taken from the literature regarding plumbagin and how to evaluate a topical formulation and skin irritation. This review is not systematic and presents no new experimental results [1, 2, 5, 6].

It is important to note that results from the crude extract, isolated compound or oral formulation should not be assumed to apply to the final formulation. Evidence should be provided for each formulation.

3 Botanical identity and phytochemical composition

3.1 Botanical identity and plant parts

Various parts of *Plumbago zeylanica* have been investigated. These include roots, root bark, leaves and stems. However, roots and root bark are the most common in the literature. Leaves have also been reported to have traditional external uses [1]. The plant is shown in Figure 1.

When creating a formulation it is important to know exactly which part of the plant you are using. Even though both leaves and roots are from the same species, they should not be assumed to be interchangeable. Information should be given on how the extract was created and what compounds are present in the extract to allow meaningful comparisons of the biological activity.



Figure 1. Plumbago zeylanica L. (Chitrak), a medicinal plant of the family Plumbaginaceae; the roots, root bark, leaves and stems have been investigated for phytochemical and pharmacological properties (image source: Wikimedia Commons, Plumbago_zeylanica1MTFL.jpg).

3.2 Key compounds

Plumbago zeylanica contains various phytochemical groups. These include naphthoquinones, flavonoids, tannins, saponins, glycosides, terpenoids, coumarins and sterols. Reported compounds include plumbagin, chitranone, chloroplumbagin and β-sitosterol [1].

The structure of plumbagin is shown in Figure 2. Because plumbagin has been studied for various biological activities it is important to consider this when creating a formulation. However, the crude extract will contain multiple potentially active compounds. Measuring the plumbagin concentration may help ensure that the formulation is consistent but will not give a full picture.

A practical approach would be to standardise using botanic identification, chromatography and quantifying the selected compounds.

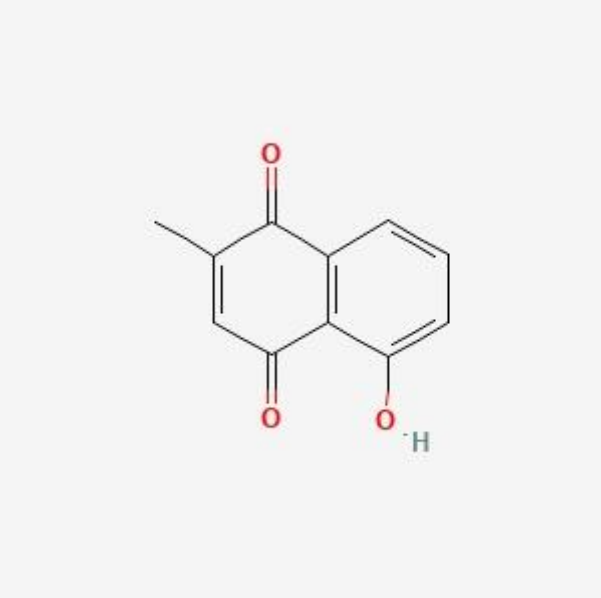


Figure 2. Chemical structure of plumbagin (C11H8O3), a major bioactive naphthoquinone constituent of Plumbago zeylanica (image source: PubChem, CID 10205).

3.3 Implications for topical formulation

Plumbagin has poor aqueous solubility meaning it can be difficult to incorporate into aqueous formulations. It can also have concentration dependent effects meaning increasing the amount in the formulation is not always beneficial [2].

It is therefore important to consider the delivery and skin tolerance. Ideally you want a formulation that will provide an appropriate level of exposure along with acceptable skin tolerance.

4 Scientific rationale

4.1 Antimicrobial activity

The literature has shown that extracts from various parts of *Plumbago zeylanica* have antimicrobial activity. Different organisms have been looked at such as Staphylococcus aureus and Pseudomonas aeruginosa. However different extraction methods, concentrations and testing methods were used so it is difficult to compare results [1].

This shows that further research could be done. However, there is no guarantee that any cream or ointment will be able to effectively treat a skin infection. The final formulation should be tested as the excipient may affect how much is available.

4.2 Anti-inflammatory activity

Experimental studies have shown anti-inflammatory activity. However some of these studies used oral administration and animal models. This makes the evidence relevant to the pharmacological potential but is not directly relevant to a topical formulation [1].

Studies have also been carried out on plumbagin and its effects on inflammatory pathways such as NF-κB and MAPK. This can be useful to help determine appropriate endpoints but should not be seen as evidence that it will be beneficial for inflammatory skin diseases.

4.3 Antioxidant activity

Extracts of *Plumbago zeylanica* have shown antioxidant activity in laboratory tests. The response will depend on extraction method and type of assay [1].

This information is useful for initial screening but will not indicate if the formulation will provide protection to live skin. This is especially important as plumbagin can have pro-oxidant effects. The results should be considered alongside cell viability and tissue compatibility [2].

4.4 Wound healing

One of the more relevant areas to look at in relation to topical use would be wound healing. In an animal study a 10% w/w methanolic root extract ointment was associated with increased wound contraction and reduced healing time [1].

However, this is referring to the crude extract and not pure plumbagin. This should not be assumed to be the concentration used in humans. More work would be needed to create a reproducible formulation and to ensure that the benefits outweigh the risks.

5 Choosing an appropriate topical formulation

You may want to look at creating an ointment, cream, gel or emulgel. The choice depends on what you want to use the formulation for and what the extract will be like. The main development question for each dosage form is summarised in Table 1.

Table 1. Main development question for each candidate topical dosage form.

Dosage form	Main question during development
Ointment	Is the extract evenly dispersed and is it reproducible?
Cream	Is the emulsion stable?
Gel	Is the extract evenly dispersed?
Emulgel	Is the formulation consistent?
Advanced delivery system	Has the increased complexity provided any improvement in delivery, safety or stability?

These are suggestions for what you may want to try when creating your formulation. They should not be assumed to be validated for *Plumbago zeylanica*. They should be assessed using established principles for evaluating topical formulations [3, 4].

6 Evaluating the final formulation

6.1 Identification and standardisation

The first thing to consider would be the quality of the raw material. Information should be given on the botanic identity, part of the plant used, source of the plant and how it was extracted. The extract should also be characterised.

The formulation should state clearly how much crude extract and how much of the selected marker was present. This is important as there are various parts of the plant, extracts and isolated compounds mentioned in the literature. Without knowing what you started with it will be difficult to compare formulations [1].

6.2 Appearance

The formulation should be checked for colour, smell, texture, grit, particulates, crystals and phase separation.

However this should not be the only thing considered. Even if the formulation looks smooth it may not be consistent. Appropriate sampling and analysis should be carried out. Appearance, phase and particle are recognised factors to consider when evaluating a topical formulation [3, 4].

6.3 pH

If the formulation contains any aqueous components the pH should be measured. This should be clearly stated how it was carried out. Any temperature, sample preparation or dilution should be stated.

The pH range should be justified for the formulation. It should not just be stated as a typical pH for skin. Local tolerance and formulation stability should be considered. The FDA have highlighted that differences in pH can be relevant to irritation and topical performance [4, 7].

6.4 Rheology

Rheology will tell you how the formulation flows and how it behaves under force. Viscosity may not be very informative.

If appropriate you should look at the viscosity under various shear rates, flow behaviour, yield point and shear thinning. More detailed information can also be gained by looking at the viscoelastic properties. This will help characterise the formulation [3].

Spreadability and extrudability can give extra practical information. Careful consideration should be given to how this was carried out. What apparatus was used, what force was applied, what temperature and how long was it carried out for.

6.5 Marker content

A suitable analytical technique should be used to determine how much of the selected marker is present. This will ensure that the compound can be reliably extracted from the formulation. There should be no unacceptable interference from the excipient.

Sampling should be carried out to ensure that the marker is evenly distributed throughout. The formulation should be reported to show how much of the extract was present, how much of the marker was present in the extract and how much was present in the final formulation. This will help

avoid confusion about whether the formulation is made from crude extract or purified plumbagin [1, 2].

6.6 *In vitro* release

The release of a measured compound from the formulation should be carried out. This should state what membrane was used, receptor solution, diffusion area, temperature, sampling and analytical technique.

This can help compare different prototype formulations or see if there are any changes when the formulation is stored. It does not tell you that the compound will be delivered to the required area within live skin. Release and permeation are different [4, 8]. The principle is illustrated in Figure 3.

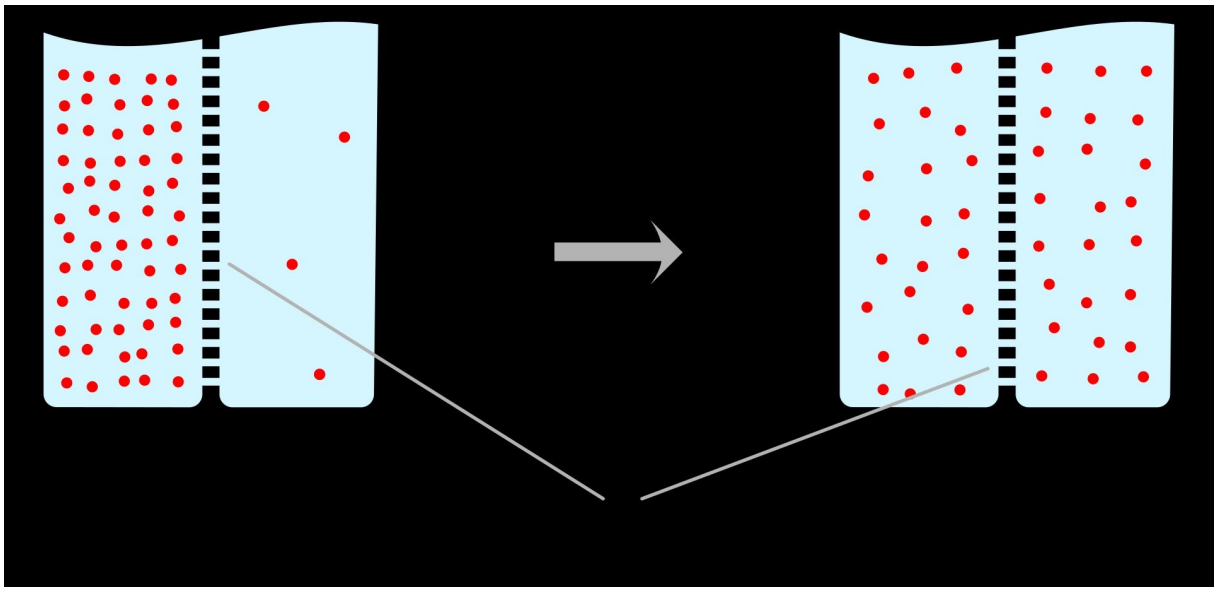


Figure 3. Diffusion across a semipermeable membrane, illustrating the principle of in vitro release and permeation studies (image source: Wikimedia Commons, Diffusion.en.svg).

6.7 Skin distribution

Consider how much of the formulation will stay on the surface, how much will be absorbed into the skin and how much will be absorbed past the skin.

When creating a topical formulation with a local effect it is not always best to have high permeation. You want an appropriate concentration to reach the target site and have acceptable tissue compatibility. This is particularly important for plumbagin as it has concentration dependent effects [2].

7 Biological evaluation

7.1 Antimicrobial activity of the formulation

The final formulation should be tested alongside the vehicle, standardised extract and an appropriate control. This will help determine if the effect is due to the plant material, excipient or both.

If you only test the extract you will not know if the final formulation will maintain and deliver the activity. As there is a lot of variability in the extract studies this is very important to consider [1].

7.2 Anti-inflammatory activity of the formulation

Skin relevant models should be used to investigate any inflammatory effects. Cell/tissue viability should be measured.

Reducing an inflammatory marker may not be beneficial if it is due to the cells being damaged. Plumbagin has concentration dependent effects so this is essential to consider [2].

7.3 Wound healing activity of the formulation

Appropriate endpoints should be chosen. This can include cell migration, wound contraction, epithelialisation, tissue organisation and compatibility with the wound environment.

The formulation should also be tested alongside the vehicle as a control. There is evidence from animal studies to suggest further investigation could be done but controlled studies should be carried out on the final formulation [1].

8 Skin safety

Traditionally used does not guarantee that it will be safe. The literature has shown that there are biological effects and toxicological concerns with *Plumbago zeylanica* and plumbagin. The systemic findings cannot be directly linked to the topical risk but it highlights the importance of testing for exposure specific effects [1, 2].

A safety plan should be created to consider irritation, tissue compatibility, sensitisation, repeated exposure and systemic absorption.

OECD Test Guideline 439 states how to identify skin irritation hazards using a reconstructed human epidermis. This can be part of a wider testing plan but a satisfactory result will not guarantee total safety in a clinical setting or that it will not cause any adverse effects [6].

Human studies should be carried out after a suitable pre-clinical evaluation and with appropriate ethical approval. Unvalidated formulations should not be presented as established treatments.

9 Stability

The stability of the formulation should be tested using the packaging it will be sold in. This should not just consider visual changes but also what is happening chemically.

A stability plan should be created to look at:

- **Appearance** – Are there any changes?
- **Phase separation** – Is there any phase separation?
- **Crystals** – Are there any crystals?
- **pH** – What is the pH?
- **Rheology** – How is the rheology?
- **Marker content** – What is the marker content? Are there any relevant changes?
- **Particles/globules** – Are there any particles/globules?
- **Release** – How is the release?
- **Appropriate microbial quality** – What is the microbial quality?

These are recognised factors to consider when evaluating a topical formulation. This is a suggestion of what should be considered [3, 4].

10 Limitations and future work

The main limitation to the evidence is that there is a lot of variability. Different parts of the plant, solvents, extracts, doses, routes of administration and models have been used. This means that findings may not be comparable as they could be very different formulations. Most of the evidence is also pre-clinical.

Future work should be more focussed. Decide what indication you want to target, standardise the extract, decide what formulation to use, ensure it is reproducible and link the delivery to biological activity and safety.

Particular consideration should be given to how to ensure it is effective but not damaging. Plumbagin has poor aqueous solubility and concentration dependent effects so any improvements in delivery should always be assessed with regards to the skin tolerance [2].

Clinical investigations should only be carried out once the formulation has a clear quality and safety profile.

11 Conclusion

Plumbago zeylanica has a reasonable basis to carry out further investigations into a topical formulation. It has traditionally been used externally and has shown antimicrobial, anti-inflammatory, antioxidant and wound-healing activity in experimental studies. However there is no evidence to show that there is a universally safe concentration or a clinically validated topical formulation [1, 2].

To create a meaningful formulation you need to ensure that the final formulation is chemically consistent, physically stable, reproducible and acceptable to the skin. This will depend on bringing all of these factors together.

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