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Review Article

Flower-Color Variation and Solvent-Dependent Phytochemistry of *Lantana camara*: Implications for Wound-Healing Hydrogels

Priyanshu Jakhmola[1], Navinraj Dudhnath Mourya[2*]

[2] B. Pharm, School of Pharmacy, Rai University, Ahmedabad, Gujarat – 382260, India.
[2] Associate Professor, Department of Pharmaceutical Quality Assurance, School of Pharmacy, Rai University, Ahmedabad, Gujarat – 382260, India.

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ABSTRACT

Lantana camara L. (Verbenaceae) is used traditionally to treat wounds and skin disorders. The inflorescences display a variety of colours within different morphotypes such as white, pink, yellow, orange, and red. This variation is largely attributed to differences in anthocyanin and carotenoids; however, no significant differences in overall phytochemical groupings were found between flower morphologies using GC-MS. Essential oils extracted from different morphologies showed varying chemical profiles and antiproliferative activity. Phytochemical profiles and activity of L. camara are greatly influenced by the choice of solvent. Polar solvents, such as methanol and aqueous/alcoholic mixtures, were found to give promising results when extracting from L. camara in terms of yield, phenolics, flavonoids and antioxidant/antimicrobial activity. Topical agents containing L. camara extracts have been found to show increased wound healing in excision and diabetic rodent wound models. However, positive effects were not observed in burn wounds. Hydrogels provide promising delivery vehicles for plant extracts due to their water retaining capabilities, biocompatibility, and adaptability. Systematic studies correlating flower colour morphology, solvent dependent phytochemistry and hydrogel efficacy in wound healing applications are lacking. This review investigates the characteristics, phytochemistry and extraction methods of L. camara, and wound healing potential. A proposed method is presented for producing wound healing hydrogels specific to flower colour morphotype and solvent type. Potential toxicity of lantadene compounds is discussed, and areas for future research are highlighted.

***Corresponding Author:** Navinraj Dudhnath Mourya
Address: B. Pharm, School of Pharmacy, Rai University, Ahmedabad, Gujarat – 382260, India.
Email ✉: priyanshujakhmola15@gmail.com
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INTRODUCTION

Chronic wounds are an ongoing burden, with diabetic patients particularly vulnerable due to prolonged inflammation, poor angiogenesis and increased oxidative stress [14]. Current treatments such as wound dressings and topical antibiotics do not fully solve the issue and due to increasing antibiotic resistance there is a push back to using botanically derived wound treatments, providing a broad spectrum of antimicrobial, antioxidant and anti-inflammatory properties within one material [11,12] .Many cultures have historically used medicinal plants to treat wounds, with recent developments looking at producing hydrogels containing plant extracts to maintain a moist wound environment, absorb exudate and provide controlled delivery of active compounds [11,13] .

One of the most prominent and paradoxical plants that can be used for this is Lantana camara L.. Whilst this plant is listed as one of the hundred worst invasive species globally [1] and was brought into India as an ornamental plant in the early 19 th century [1] ,it is very plentiful, readily available and inexpensive making it a good source of active compounds for wound treatment [10] .In folk medicine the leaves are used as an antiseptic for wound healing and treating itch. It can also be applied externally to treat skin conditions [7] . The plant contains many active compounds including triterpenoids, flavonoids, phenylethanoid glycosides, iridoid glycosides, sesquiterpenes and phenolic acids. However, there is well documented toxicity from the pentacyclic triterpenes found in the plant known as lantadenes to grazing animals [15-18] .

However, there are factors to consider when extracting compounds from this plant. Firstly, L. camara is a complex species with lots of variation between both horticultural and wild variants. One of the most obvious variations is the colour of the flowers. This isn't a trivial change, it is an indicator of the pigments being produced in the plant. Variation in flower Colour has been linked to differences in pollination and invasion [1,2] .There have only been a few studies into whether variations in flower Colour will result in variations in the active portion of the plant such as phenolics, flavonoids and volatile terpenoids [1,3,4] .Secondly, the solvent used to extract the compounds will affect what compounds are extracted, how much of each compound is extracted and therefore what biological activities can be seen [4,5] . This will also affect how compatible the extract is with the hydrogel polymer, stability and delivery [11] .

This review will firstly provide an overview of the botany of L. camara and how it became an invasive species. It will then look at the types of phytochemicals reported from different parts of the plant. There is little evidence to show there is variation in the plant based on flower Colour. The effect of solvent used to extract the compounds will be discussed in detail. Pre-clinical wound healing studies will be summarised and an overview of how plant extracts can be added into hydrogel dressings will be provided. A practical method will be proposed for creating L. camara hydrogels based on the flower Colour and solvent used. Considerations around safety will be highlighted along with the key areas that need to be improved to consider translating these. This is a narrative review using only 20 sources. Therefore it should be considered as a guide and research area rather than a systematic meta-analysis.

2. Botany, Distribution and Invasion Biology

Lantana camara (Verbenaceae) is an invasive plant native to the tropical areas of the Americas, but has become invasive throughout Africa, Asia and Australasia [15,18] .The plant is a perennial, highly branched shrub with aromatic opposite leaves. Dense terminal clusters of small tubular flowers emerge followed by fleshy ripe fruit changing from green to blue-black. There are many cultivars and varieties of this plant (hundreds in total) and they vary in growth habit, leaf characteristics and flower colour [10,17] .L. camara was introduced to India in the early 19 th century. Its success in this region can be attributed to its ecological suitability, reproductive strategy, high biomass production, litter production and allelopathy of surrounding native flora [1] .

Lantana camara's pollination biology is essential to understand why different colour morphs exist. Field studies were carried out investigating three different morphs in South India. Twenty different pollinators were found to visit the flowers. Sixteen of these

pollinators were butterflies; three bees and one moth. Some of these pollinators visited multiple morphs whereas others had a preference for one colour morph [1] .Previous studies have shown that L. camara populations pollinated by thrips have strong colour discrimination with colour variation occurring post pollination [2] . As a medicinal chemist, it is important to know this information as it explains why L. camara is chemically and visually diverse in natural populations. This means that plants collected at different times of year, or from different locations may not be chemically identical. There has been a proposal to standardise L. camara flowers using pharmacognostical methods, looking at macroscopic and microscopic features along with extractive values, ash values and loss on drying following WHO guidelines [20] .

As an invasive plant it is generally thought to be an ecologically neutral or positive practice to harvest L. camara for medicinal use in invaded regions [18] However, L. camara is a toxic plant and the toxic load must be addressed when developing any therapeutic uses.

3. Flower Colour Polymorphism and Its Pigment Basis

The most obvious changeable trait of L. camara is the flower colour. Inflorescences display many different colours including pink or red buds, yellow recently opened flowers and orange, scarlet or magenta mature flowers [2] . This is due to the flowers responding to a co-ordinated developmental programme. Pigment analysis showed that the main pigments are delphinidin monoglucoside (anthocyanin) and β-carotene (carotenoid) [2],Carotenoids give the flower a yellow colour when first opened. As they age they turn orange, scarlet and magenta, this is because the anthocyanins are increasing. This means that the anthocyanins are masking the carotenoids [2].

Interestingly, the anthocyanin production was triggered by pollination. Having as little as one grain of pollen on the stigma of a yellow flower triggered flower colour change. Injecting a pollen suspension into flowers that were opened in vitro caused pigmentation changes. Pollen extract could also cause the same effect of pollination, this suggests a pollen component is involved [2] .Thrips are only attracted to yellow flowers, therefore flower colour change is a signal to attract pollinators to the unpollinated flowers, saving their energy [2] . This information is useful to myself in this review as it shows that there is a lot of variation in the colour of L. camara. Each flower of the same plant will have varying pigments depending on how old they are and if they have been pollinated. Even flowers within the same inflorescence will have differing pigments.

3.1 Why pigment chemistry matters for wound-care materials

Anthocyanins are water soluble pigments of the flavonoid class. Carotenoids are lipid soluble isoprenoids. This difference in polarity means they will have very different solubility within the same solvent, as discussed in section 6. Both are generally associated with antioxidant activity. Flavonoids are one of the most frequently reported compound groups with antioxidant, anti-inflammatory and pro-angiogenic properties[14]. Therefore it is reasonable to hypothesise that flowers with high anthocyanin content (dark pink/red) and those with high carotenoid content (yellow), will produce extracts with differing polarity and antioxidant capacity. However this has not yet been investigated, studies have been carried out into colour related chemistry but either focused on volatile or semi volatile metabolites[1,3], or were not directly comparing pigmented extracts. A simple experiment could be conducted to quantify the different pigment classes along with total phenolics and flavonoids in each morph using standard extraction.

Furthermore, pigmentation can be an easy way to determine quality. The flower colour can easily be determined by eye or a simple colourimeter. As the colour depends on genotype and development[2], recording the morph and age of the flower would provide useful extra data when using the extract in a biomedical setting.

4. Phytochemical Constituents of Lantana camara

L. camara's chemical composition has been extensively reviewed. It has been found that this plant exhibits great chemical diversity, with an extensive review into its ethnopharmacology, phytochemistry and toxicology categorising them into triterpenes, iridoid glycosides, furanonaphthoquinones, flavonoids and phenylethanoid glycosides[16]. A more recent review

into the genus identified that the most prominent secondary metabolites in Lantana species are terpenoids, flavonoids and phenylpropanoids. Non toxic species do not contain any lantadenes[17]. Further recent reviews have identified sesquiterpenoids, alkaloids and phenolic acids, with bioactive compounds including humulene, caryophyllene, apigenin, quercetin and epicatechin identified from different parts of the plant[18]. Another review identified ursolic acid, oleanolic acid, linaroside, lantanoside, verbascoside, camarinic acid, phytol, and umuhengerin can be isolated. This plant also contains saponins, alkaloids, tannins, anthocyanins, flavones, isoflavones, coumarins, lignans and catechins[15].

4.1 Compound classes relevant to wound healing

Several constituents within the plant are of interest for wound healing. Verbascoside, a phenylethanoid glycoside, has been reported in L. camara and is mentioned in medicinal reviews of L. camara as being one of the characteristic bioactive compounds[15,19]. Flavonoids such as apigenin, quercetin and epicatechin (a catechin type) are polyphenols. In general these compounds have antioxidant effects (scavenging reactive oxygen species) and can modulate inflammatory pathways which are clearly relevant to chronic wounds[14,18]. Pentacyclic triterpenoids such as ursolic and oleanolic acid are lipid soluble compounds often looked at for having anti-inflammatory actions[15]. Sesquiterpenes such as caryophyllene and humulene are found in high concentrations within the volatile fraction of the plant and are associated with antimicrobial and anti-inflammatory effects[18].

4.2 Compounds that limit therapeutic use

Lantadene A and B are pentacyclic triterpenoids which are mainly present in the leaves and green berries of L.camara. These compounds cause liver toxicity and photosensitisation in sheep, cattle and other animals[15,16]. Unripe berries have also been linked to causing death in humans[16]. Whilst their presence in the plant would not necessarily prevent them from being used topically, it is important to determine what proportion they are present in the formulation. Extraction methods should also be considered as they have the potential to concentrate these lipid soluble triterpenoids. This will be discussed further in section 10.

4.3 Variation among plant parts and varieties

Chemical constituents differ between different plant organs. Research has been carried out on leaves, flowers, stem, roots and fruit with leaves being the most commonly used part within wound healing research[7,8,9,10]. Flower research however has not been as extensive. Leaves and flowers were compared after being extracted with methanol. They were found to be rich in phenolics and flavonoids and show antioxidant activity, making them a good source to use as a raw material in herbal products[6]. Different solvent experiments also show significant differences between flower and leaf samples. The flowers had significantly different levels of phenolics and flavonoids and antioxidant activity compared to the leaves[5]. Different varieties have also been shown to have different phytoconstituents. Methanolic extracts of 4 Indian varieties of leaves have shown differences in their antioxidant properties[4]. Overall, it shows that all 3 factors will affect the results. Therefore if only one factor is varied in research then it will not give a full picture.

5. Does Flower Colour Predict Chemistry? Evidence from Morph-Level Studies

If flower colour is to be used as a useful character to select raw material then it must correlate with chemically significant differences. Two recent studies have been carried out which give some interesting conflicting results.

5.1 Floral secondary metabolites by GC–MS

Metabolite profiles were obtained using GC-MS (methanol extraction and derivatization) of bud and day one and two flowers of the dark pink, white pink, and orange red morphs collected from three locations around Madurai, India[1]. In total 72 metabolites across 10 chemical classes were observed, with the dark pink morph having 39, white pink 36, and orange red 37. The major classes were benzenoids, organics containing oxygen, hydrocarbons and lipids/lipid like. Using one way ANOVA no significant differences were seen between morphs in terms of the number of metabolites from each chemical class. This was also true in terms of insect semiochemicals. However, there were a few unique compounds in each morph. Heptadecane was only in the dark pink morph; in the white pink morph there was a cluster of compounds, including dimethylbenzene, ethylbenzaldehyde, nonadecane, triacontane and two fatty acid methyl esters. The orange red morph had octacosane, hexatriacontane and two fatty acid methyl esters[1]. Of the 72 metabolites 22 were annotated as insect semiochemicals. The abundance of the dominant pollinator did not significantly correlate with the number of associated semiochemicals.

At the general chemical class level the three morphs were statistically similar[1]. However differences in the actual compound types can be seen. These are largely alkanes, fatty acid esters and low molecular weight aromatics, which are typically found in volatile and semi-volatile fractions. There are not many polyphenols, which are the most important for antioxidant and wound healing activity[1]. Finally the GC-MS method used was polar derivatized meaning that anthocyanins and larger flavanoid glycosides will not be observed. This means that no differences between the different colour classes are seen in this data set, so it is difficult to make any statements on the polyphenol content[1].

5.2 Essential oils from white, pink and orange flowers

The chemical composition of hydrodistilled essential oils were studied using GC-MS. Antioxidant activity was determined using DPPH and FRAP assays while antiproliferative activity was also assessed against the MCF-7 and MDA-MB-231 breast cancer cell lines compared to the MCF-10A normal cell line.[3] All oils displayed significant antioxidant activity with positive correlation between antioxidant activity, total phenolic and flavonoid contents.[3] The white flower oil displayed the most significant and selective dose dependent antiproliferative activity due to the presence of bicyclogermacrene and epi-bicyclosesquiphellandrene in the chemical composition.[3] This study provides the most clear evidence of colour related differences in chemical composition and biological activity of an L. camara extract. However, this study looked at anticancer activity rather than wound healing and the oil is a specific lipophilic fraction.

5.3 Interpretation

There is no contradiction between these two studies. The first study showed no significant quantitative difference between total numbers of each chemical class within metabolites detected by a single analytical method. The second study showed activity to depend on the composition of whole essential oils[1,3]. This suggests that the colour morphs have a general similarity in their chemical profile but have different ratios of certain compounds. A key point to consider with respect to wound healing development is whether there is a difference in the concentration of antioxidant and antimicrobial compounds in the solvent fraction to be incorporated into the hydrogel. This has not yet been investigated for polar extracts and should be a priority.

6. Solvent-Dependent Phytochemistry and Bioactivity

Extraction is where the variety of chemicals within the plant are isolated. Depending on the solvent used (polarity), different compounds will be extracted. Polar solvents (water, methanol, ethanol) generally extract water soluble/medium compounds (phenolics, flavonoids), and non-polar solvents will extract more lipid soluble compounds (terpenoids, fatty components). This can be seen in experiments on L. camara.

6.1 Leaf extracts across solvents of different polarity

The leaves were extracted using ethyl acetate, methanol, acetone and chloroform[4]. Methanol provided the highest percentage of extractable matter

(14.4%), phenolics (92.8 mg gallic acid equivalents g-1) and flavonoids (26.5 mg rutin equivalents g-1). The methanol extract had the lowest IC50 value in the DPPH assay (165 µg/mL), with ethyl acetate (200 µg/mL), acetone (245 µg/mL) and chloroform (440 µg/mL) providing higher values[4]. This was mirrored in the hydroxyl radical assay where methanol had the lowest IC50 (110 µg/mL), ethyl acetate (240 µg/mL), acetone (300 µg/mL) and chloroform (510 µg/mL)[4]. As it was the most polar extract it contained the highest concentration of phenolics and was therefore the best antioxidant. The antibacterial activity showed a similar trend with methanol providing the highest inhibition of all microbes. Gram-negative bacteria such as Escherichia coli and Klebsiella pneumoniae were more susceptible to the extract than Gram-positive species[4]. The methanol extract was analysed using GC-MS revealing 32 bioactive compounds including hexadecanoic acid, phytol and caryophyllene oxide[4].

6.2 Flowers versus leaves and the effect of water content in the solvent

The extraction of flowers and leaves using 80% methanol, 80% ethanol, absolute methanol and absolute ethanol showed significant differences in phenolic and flavonoid content and antioxidant activity between solvents and plant parts[5]. The optimum conditions were achieved when extracting the flowers with 80% methanol obtaining a total phenolic content of 21.4 g gallic acid equivalents/100g, total flavonoids of 13.8 g catechin equivalents/100g, DPPH radical scavenging of 72.3% and linoleic acid peroxidation inhibition of 83.3%[5]. This is interesting, because the alcohol/water mixture gave better results than the absolute alcohols. As it can be seen the moderate water content aids in the extraction of polar glycosylated flavonoids and anthocyanin type pigments. In another study methanolic extracts were used and flowers and leaves were found to have high levels of phenolics, flavonoids and activity in radical scavenging assays[6].

Table 1: Solvent Comparison

Source	Plant part/ method	Solvents compared	Main finding
[4]	Leaves Solvent extraction	Ethyl acetate, methanol, acetone, chloroform	Methanol resulted in highest yield (14.4%) with the highest TPC value (92.8 mg GAE/g) and TFC value (26.5 mg RE/g). The DPPH IC50 value was 165 µg/mL compared to chloroform (440 µg/mL).
[5]	Flowers and leaves	80% and absolute methanol, 80% and absolute ethanol	The best extract was obtained using 80% methanol from flowers. It had the highest TPC (21.4 g GAE/ 100g DW), TFC (13.8 g CE/100 g DW) and DPPH (72.3%).
[6]	Leaves and flowers	Methanol	Both components were high in phenolics and flavonoids and showed antioxidant activity.
[3]	White, pink and orange flowers Hydrodistillation	Essential oil (volatile component	Each colour had a different composition. The white flower essential oil showed the most selectivity towards breast cancer cells. Antioxidant activity correlated with phenolics and flavonoid content.
[10]	Leaves Soxhlet	Aqueous and methanol	The methanol extract at 100mg/mL showed the best wound contraction activity on Candida infected wounds.

6.3 Implications of solvent choice for downstream use

In summary these data can be used to suggest four practical considerations when designing an antioxidant rich extract (phenolics and flavonoids). Firstly, polar solvents or aqueous alcohol mixtures are preferable to chloroform, acetone and ethyl acetate[4,5]. Secondly, polar solvents have a greater likelihood of extracting anthocyanin type pigments. This may be of importance if colour morphs are being compared. Thirdly, consideration must be given to toxicity and maximum allowable solvent residues. Methanol gave the highest recoveries, however would not be ideal for a product that will come into contact with open wounds. Ethanol or aqueous ethanol mixtures would be more

appropriate or careful removal of solvent and testing of residues. Finally, no single solvent will extract all components. Polar extracts and essential oils are complementary fractions. Phenolics will be extracted in the polar extracts and volatile terpenoids like bicyclogermacrene[3,4] will be extracted in the essential oil.

Overall, whilst the data from these extraction experiments shows us that increasing yields, total phenolic content and radical scavenging activity in vitro does not necessarily indicate that an extract will have a wound healing effect. The Folin-Ciocalteu assay will detect any reducing compound and the DPPH assay is purely a chemical indicator. The data from the studies should only be used to identify potential extracts to take forward for further biological testing.

7. Wound Healing: Biology and Evidence for Lantana camara

Overall these results can be used to draw some practical conclusions. Firstly if the aim is to produce an antioxidant rich in phenolics and flavonoids then polar solvents and aqueous alcohols are preferred to chloroform, acetone and ethyl acetate[4,5]. Secondly more polar solvents will result in higher recoveries of anthocyanin like pigments. This may be useful if comparing different coloured morphs. Methanol provided the highest recoveries in the studies above however it would be a poor choice for an extract coming into contact with open wounds. Ethanol or aqueous ethanol systems would be better options. Rigorous solvent removal and analysis should be carried out to ensure low solvent residues. Lastly there is no one solvent to take everything. Polar extracts and essential oils are complementary. Polar extracts contain phenolics whereas essential oils contain more volatile terpenoids such as bicyclogermacrene[3,4].

Overall all the extract data should be taken with caution. The extracts will not necessarily be effective at healing wounds based on their yields, total phenolic content and test tube radical scavenging activity. Folin-Ciocalteu assays react to any reducing compound present. DPPH inhibition is also a chemical based assay. The data from these studies would be best used as a guide to determine which extract to select for further biological testing.

7.1 The wound-healing process

Healing of wounds occurs in stages of hemostasis, inflammation, proliferation and remodelling[12]. Chronic wounds such as diabetic ulcers are associated with a prolonged inflammatory stage and incomplete granulation. Biofilms are an underlying cause of non-healing seen in many ulcers[12,14]. The ideal treatment would provide antimicrobial activity, reducing oxidative stress and inflammation whilst encouraging cell proliferation and collagen deposition. The wound should be kept moist[11,12]. Plant extracts can be an attractive option with one extract being able to target multiple points. However, this can make standardisation difficult[11].

7.2 Preclinical studies of L. camara

The most well known study used a topical aqueous leaf extract (100 mg/kg/day) in excision wounds on rats. It was found that the treated wounds had a 98% wound contraction rate, increased collagen production and reduced mean healing time. The extract had antimicrobial properties towards the microorganisms tested[7]. Ethanolic extract of 10%, 15% and 20% in ointment form was used in streptozotocin induced diabetic rats. It was found that increased wound contraction occurred in a concentration dependent manner. The highest concentration of extract produced the greatest effect, but it was found that wound contraction was increased mainly in the latter stages of healing. The study was notable as diabetic wounds are a main target for advanced hydrogel dressings[14].

However, when using the extract in burn wounds on rats it was found that the extract had antimicrobial properties towards Staphylococcus aureus, Klebsiella pneumoniae and Escherichia coli. However, wounds treated with the extract had similar healing times taking around 21 days. It was concluded that the plant had antimicrobial properties but did not aid healing of burns[8]. A more recent study using L. camara var. montevidensis looked at aqueous and methanolic Soxhlet extracts. It was used against Candida isolates from infected wounds and it was found that the methanol extract (100 mg/mL) had the best mean wound contraction on rats (70.3 ± 0.58). Wounds healed with the repair of damaged tissues[10].

Table 2: Preclinical Wound-Healing Studies of *L. Camara* Extracts.

Source	Model	Extract / dose	Outcome
[7]	Excision wound rat	Aqueous leaf extract topically (100mg/kg/day)	98% wound contraction. Increase in collagen. Faster wound healing. Antimicrobia
[8]	Burn rat	Leaf extract	Antimicrobial activity (S.aureus, K.pneumoniae, E.coli). Wound healing took approximately 21 days. No difference between treatment and control.
[9]	Diabetic excision rat	Ethanolic extract in ointment (10/15/20%)	Dose dependent wound contraction. Faster epithelisation. 20% most effective. Effects seen predominantly in later stages of healing.
[10]	Candida-infected rat	Methanol and aqueous leaf extract (25/50/100mg/mL)	100mg/mL methanol extract showed mean wound contraction of 70.3±0.58. Antifungal activity.

7.3 What the evidence does and does not show

Overall the studies indicate that topical application of L. camara extracts can help accelerate excision, diabetic and fungal wound healing due to their antibacterial, antioxidant and pro-collagen properties[7,9,10]. However, the negative results obtained from burn wounds indicates that healing is dependant on the model used[8]. The studies do have some issues. They all used leaf parts and were carried out on rodent models. This means they cannot be directly compared with each other as they have been extracted with different solvents from different plant parts. None of the studies carried out any chemical analysis to know what the active fraction was. None of them looked into colour morph either. Overall there is no direct evidence to suggest flower extracts help with wound healing. Flowers are chemically rich[5,6], however they are the most variable part of the plant as they come in colour morphs[1-3].

8. Hydrogels as Carriers for Plant Extracts

Hydrogels are 3D, water-swollen polymers that provide several benefits for wound dressings which are compatible with botanical actives. This includes providing a moist environment, absorbing wound exudate, being non-sticky reducing patient pain and acting as a depot system for controlled drug release[11,12,14]. Reviews have shown that hydrogels containing natural extracts enhance healing by working synergistically to reduce inflammation, provide antimicrobial activity, maintain a moisture balance and aid tissue regeneration[11].

8.1 Polymer choices

Polysaccharide based hydrogels are ideal drug delivery systems for herbal extracts. The highly connected network structure and their inherent biological properties allow a good drug delivery system for topical and oral administration. The physicochemical properties of the polysaccharide and botanical extract will affect the properties of the hydrogel, and thus the stages of healing[13]. Natural polymers including collagen, alginate and cellulose have been used to encapsulate flavonoids and small molecules for wound healing in diabetics. These hydrogels and films have antibacterial, antioxidant, and anti-inflammatory effects[14]. Films and hydrogels containing plant extracts have been reviewed for the use of essential oils and extracts. They describe the mechanism of action and what areas of research are still needed[12].

8.2 Incorporation strategies and stability

The method by which the extract is incorporated into the hydrogel can affect its stability and activity. A number of methods have been developed including incorporating the extract directly into the gel during preparation, or loading the extract into a preformed gel. Another method is to nano/microencapsulate the extract to increase stability of bioactive molecules within the hydrogel[11]. However many challenges have been faced in terms of standardising extraction processes and ensuring reproducible bioactivity of the extract

within the hydrogel system. Also standard vs non-standard extracts were noted[11]. Hydrophobic molecules, such as terpenoids and carotenoids are difficult to distribute within a water rich matrix and will often be encapsulated using micelles, liposomes or cyclodextrins. Hydrophilic compounds such as polyphenolics and anthocyanin type pigments display good dispersion and solubility but can be sensitive to pH, oxygen and light.

8.3 Relevance to diabetic and infected wounds

As the best data available for L. camara relate to diabetic and infected wounds[9,10] this would be the most logical application. In diabetic wounds high levels of glucose cause oxidative stress and chronic inflammation. This has led to the development of natural bioactive hydrogels to combat this with antibacterial, antioxidant properties and regulation of inflammation[14]. Extracts rich in phenolics and flavonoids such as methanolic and aqueous alcoholic extracts of L. camara[4,5] would fit this criteria. The proven antimicrobial activity against Gram negative bacteria and Candida also makes it suitable for wounds prone to infection[4,10].

9. A Colour- and Solvent-Guided Framework for L. camara Hydrogel Development

This evidence does not support any conclusion on the superiority of a particular colour morph, but does show that it would be beneficial to design experiments that explicitly consider the effect of colour and solvent as variables. Using the evidence from the literature, the following framework could be considered. This has not been confirmed by experimentation.

9.1 Stage 1: Raw-material definition

Collection of defined flower (and leaf) colour morphs. Record information about age, location, season and phenological phase of collection because pigment composition will vary. Collect samples that have been authenticated according to pharmacognostic standards including extractive, ash and loss on drying values[20]. Design experiment to collect samples of different age from each morph. Flower morphs will vary chemically according to age (buds, newly opened flowers, old flowers)[1,2]

9.2 Stage 2: Parallel extraction

Use a range of 3 different solvents of varying polarity (i.e. water, 70-80% EtOH and intermediate polarity such as ethyl acetate) alongside the hydrodistilled essential oil. Polar extracts and volatile fractions are complimentary in extraction[3-5]. If Methanol is needed for analysis, this can be replaced with ethanol or aqueous ethanol solutions. However, residual solvent analysis will be required. Aqueous alcohols were found to give better results than absolute alcohols when extracting L. camara flowers in one study[5], therefore aqueous fraction should be considered as a variable.

9.3 Stage 3: Chemical and in vitro screening

Determine total phenolic and flavonoid concentrations. Perform pigment specific analysis of anthocyanins and carotenoids. Characterise extracts by using LC-MS and GC-MS to detect polar metabolites. Volatile metabolites can only be detected by GC-MS[1,4]. Multiple antioxidant assays should be carried out. Antimicrobial properties should be tested against a variety of bacteria commonly found in wounds including S. aureus, E. coli, K. pneumoniae and Candida[4,8,10]. Quantify the levels of lantadene in the extracts to assess the level of safety[15,16]. Rank the extracts based on the activities they have in comparison to the levels of toxicants present.

9.4 Stage 4: Hydrogel formulation

A suitable exuding wound polysaccharide/protein matrix (e.g. alginate or cellulose based gels) should be chosen[13,14]. If using a polar extract then just add to the matrix however if using a lipophilic extract encapsulate the compound. Characterise the matrix by swelling properties, gel fraction, rheological properties, extract release and stability during storage and under physiological conditions. The main issues with these matrices are stability and reproducibility[11].

9.5 Stage 5: Biological validation

A suitable exuding wound polysaccharide/protein matrix (e.g. alginate or cellulose based gels) should be chosen[13,14]. If using a polar extract then just add to the matrix however if using a lipophilic extract encapsulate the compound. Characterise the matrix by swelling properties, gel fraction, rheological properties, extract

release and stability during storage and under physiological conditions. The main issues with these matrices are stability and reproducibility[11].

Table 3: Proposed Decision Points in a Colour- and Solvent-Guided Development Workflow.

Stage	Key decision	Reason/Supporting evidence
Raw materials	Morphology, maturity of flower, geographical origin and season	Pigment and metabolite profile is affected by maturity and pollination status[1,2]
Extraction	Water, aqueous ethanol, medium polarity solvent, essential oils	Solvent polarity will effect extraction levels, TPC, TFC and activity. Essential oils vary in color[3,4,5].
Screening	TPC/TFC, pigments, LC–MS/GC–MS, antimicrobial, lantadenes	To understand the correlation between colour and chemical profile. Active fractions are identified as safe[1,4,15].
Formulation	Polymer type, loading method, stability	Standardisation and stability issues[11,13]
Validation	Excision, diabetic, infected and burn models	Prior positive and negative data[7–10]

10. Safety, Toxicity and Regulatory Considerations

Any wound product derived from L. camara must consider its toxicological effects. The hepatotoxic pentacyclic triterpenes lantadenes A and B are the most well-known toxicants from L. camara, mainly present in the leaves and green berries[15,16]. Ingestion of the unripe berries has caused poisoning in humans, with some cases proving fatal[16]. When using topically the risk of first pass metabolism is removed however wounds, particularly large/chronic wounds, will have compromised barriers. Therefore lantadene levels should be quantified in each extract and absorption and cytotoxicity assessed in an appropriate model prior to use in humans.

The material should also be as consistent as possible. Plants growing in invaded environments may have accumulated environmental toxins and therefore there can be differences in the chemical make up between different areas, times of year and varieties[4,10]. Using cultivated or standardised material will provide more consistency and using pharmacognostic techniques to control quality[20]. Any residual solvents, microbial load and allergenic potential of the plant extract and essential oil should be considered as would any other herbal dressing. As noted in reviews of natural extract hydrogels standardisation of the extraction process and consistency of bioactivity are required for effective translation[11].

Care must be taken when considering traditional use. Many reviews highlight the traditional uses of L. camara, which range from wound healing to treating cancer and skin diseases[15,18,19]. However traditional use does not mean it is safe or effective. A single study looking at burns wounds found no benefit to healing[8]. L. camara shows promise as a source of active wound care ingredients however further research is needed.

11. Research Gaps and Future Directions

There appears to be several gaps in the literature surrounding flower pigmentation. Firstly, there has been no investigation into the relationship between flower pigmentation and the polar, phenolic rich fraction. Previous works have investigated volatile compounds and essential oil fractions of the flower pigmentation morphs[1,3]. Therefore, investigating differences in antioxidant and antimicrobial properties using white, pink, yellow, orange and red morphs using the same solvent system would give controlled information regarding whether the colour of the flower can act as an indicator.

Floral extract has not been investigated within any wound models. All wound healing studies have been carried out using leaf extracts[7-10], however, the floral extracts have shown the highest phenolic and flavonoid values in at least one solvent comparison[5]. Comparing leaf extracts with flower extracts within a standardised excision wound model would be beneficial.

The effect of solvent on bioactivity within wound models has not been well investigated. Any studies that were conducted used aqueous, ethanol or methanol extracts and were carried out in different animals, concentrations and vehicles[7,9,10]. This means that antioxidant activity has not been verified within these test tube assays[4,5].

Finally, there is little information regarding hydrogel formulation of L. camara. Many other plant extracts have been well investigated within polysaccharide and protein hydrogels[11-14]. More information regarding molecular mechanisms would be beneficial. This includes inflammatory, angiogenic and collagen turnover gene/protein markers, plus measuring oxidative stress. Additionally, full toxicology studies have yet to be undertaken regarding topical application of L. camara extracts. This should include quantifying levels of lantadene and measuring dermal absorption[15,16]. There should also be standardisation within studies to allow comparison with future studies. This should include information relating to which morph, plant part, flower age, solvent, extraction conditions, yield and marker concentrations were used. As shown throughout this review there is variation within the literature[1,2,4,5,11].

CONCLUSION

The plant species Lantana camara has a diverse chemical profile and has been traditionally used as a wound healing herbal remedy. Pre-clinical evidence supports its topical effects within excision, diabetic and infected wounds[7,9,10] whilst no benefit was observed within burns[8]. There is a lack of integration between two variables; flower colour and solvent type which have been used to extract the active compounds. Flower colours are reflective of the dynamic anthocyanins and carotenoids present[2]. Chemical profiling at the morph level has shown similarity of compound types but minor differences with unique compounds and variation in essential oils[1,3]. However, there is a consistent trend of increased phenolic, flavonoid content and antioxidant activity when using more polar solvents[4,5]. Hydrogels are an established delivery system[11-14] but have not been investigated using L. camara. A colour and solvent guided method with careful toxicological consideration of the lantadenes is a logical approach to develop from a traditional remedy to a standardised evidence based wound dressing. Until this work is completed any claims regarding specific benefits due to colour should be considered hypothesis.

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