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Review Article

A Critical Appraisal of *Withania somnifera* and *Curcuma amada* Transdermal Patches for Inflammation and Pain

Nisha Purke[1*], Anjali Patil[2], Mohd Saleemuddin Farooqui[3], Sayyad Sajauddin Gulab[4], Sandip Fulzele[5]

[1] Student of Master of Pharmacy, Department of Pharmaceutics, Central India College of Pharmacy, Lonara, Nagpur, Maharashtra, India.
[2] Assistant Professor, Department of Quality Assurance, Central India College of Pharmacy, Lonara, Nagpur, Maharashtra, India.
[3] Principal, Central India College of Pharmacy, Lonara, Nagpur, Maharashtra, India.
[4] Vice Principal, Central India College of Pharmacy, Lonara, Nagpur, Maharashtra, India.
[5] Professor, Department of Pharmaceutics, Central India College of Pharmacy, Lonara, Nagpur, Maharashtra, India.

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ABSTRACT

Transdermal patches carrying extracts of Withania somnifera have been proposed as a safer alternative to oral non-steroidal anti-inflammatory drugs for localised inflammation and musculoskeletal pain. The pharmacological case is good and, unusually for a botanical, it includes direct evidence in skin: a root extract has been shown to suppress mitogen-activated protein kinase and nuclear factor kappa B signalling in human keratinocytes and to lower tumour necrosis factor alpha in a murine skin wound model. The formulation literature has not kept pace with that pharmacology. This review sets out the phytochemistry, the mechanistic evidence, the physicochemical constraints on percutaneous delivery of withanolides, the patch architecture conventionally used, and the evaluation battery conventionally applied. It then examines four problems that recur across published studies: an analytical method without specificity, a release test reported as a permeation test, a payload arithmetic that is almost never shown, and a marker assumption that the one study to look directly at skin does not support. Each is remediable, and the final sections propose what a defensible study would require.

***Corresponding Author:** Nisha Purke
Address: Student of Master of Pharmacy, Department of Pharmaceutics, Central India College of Pharmacy, Lonara, Nagpur, Maharashtra, India
Email ✉: purkenisha@gmail.com
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INTRODUCTION:

Inflammation is a protective vascular and cellular response to injury, infection or irritation, mediated by prostaglandins, cytokines, histamine, leukotrienes, bradykinin and nitric oxide. These mediators produce vasodilatation, increased vascular permeability, and the sensitisation of nociceptors that lowers the pain threshold. Where the response persists, continued cytokine and reactive oxygen species release causes tissue damage rather than repair.

Conventional management rests on non-steroidal anti-inflammatory drugs and corticosteroids. Non-steroidal agents inhibit cyclooxygenase, and because COX-1 derived prostaglandins maintain gastric mucosal integrity and renal perfusion, inhibition brings gastrointestinal, renal and cardiovascular liabilities that scale with dose and duration [1,2]. Corticosteroids suppress the cascade more broadly, at the cost of hyperglycaemia, osteoporosis, immunosuppression and adrenal suppression on prolonged use [3]. Both require repeated oral dosing for chronic conditions, exposing the whole body to achieve an effect often needed in one region.

Withania somnifera is among the most intensively studied Ayurvedic plants, and its anti-inflammatory pharmacology is better characterised than that of most botanicals proposed for topical use. The question this review addresses is not whether the plant has anti-inflammatory activity. It is whether a transdermal patch can deliver enough of the responsible constituent, through intact skin, to produce that activity, and whether the published studies claiming it have measured what they say they have measured.

WITHANIA SOMNIFERA: BOTANY AND PHYTOCHEMISTRY

W. somnifera (L.) Dunal, family Solanaceae, known as ashwagandha, Indian ginseng or winter cherry, is an erect perennial shrub of 30 to 150 cm, native to India, North Africa and the Middle East and cultivated in dry and semi-arid regions. In India it is distributed principally through Madhya Pradesh, Rajasthan, Gujarat and Maharashtra. The root is the main medicinal part; leaves and berries are also used.

The characteristic constituents are the withanolides, a family of C28 steroidal lactones built on an ergostane skeleton. Withaferin A and withanolide A are the best characterised; sitoindosides, alkaloids including withanine and somniferine, saponins and phenolic acids are also present. Root and leaf differ materially in withanolide profile, with withaferin A generally more abundant in leaf, which matters because a study that specifies only "ashwagandha extract" has not specified its chemistry.

Commercial standardised extracts typically declare total withanolides at one and a half to five per cent [4]. This figure is the single most important number in Section 8, and it is the one most often omitted from published formulation work.

ANTI-INFLAMMATORY AND ANALGESIC PHARMACOLOGY

The systemic evidence

Withaferin A carries most of the mechanistic evidence. It inhibits nuclear factor kappa B signalling, with consequent reduction in tumour necrosis factor alpha, interleukin-1 beta and interleukin-6 release, and attenuates inflammation in animal models of arthritis [5,6]. Network pharmacology analyses place multiple withanolides against cyclooxygenase-2, tumour necrosis factor alpha and interleukin targets, supporting the multi-target argument commonly made for botanical therapy [7]. The plant's effects on inflammatory signalling have been reviewed in the context of ageing and chronic low-grade inflammation [8,9].

The analgesic evidence is weaker than the anti-inflammatory evidence and is largely secondary to it: reduced oedema and reduced prostaglandin-mediated nociceptor sensitisation rather than a distinct antinociceptive mechanism. A claim of analgesia should be stated at that level.

The evidence in skin, which is the evidence that matters here

Most of the above comes from isolated withaferin A in cell culture or from oral dosing in rodents. It is evidence about the molecule and about systemic exposure, not about a topically applied extract.

One study addresses skin directly and deserves more weight in this literature than it receives. A hot-water root extract was non-toxic to HaCaT keratinocytes up

to 10 mg/mL; it reduced interleukin-8, interleukin-6 and interleukin-12 messenger RNA dose-dependently, lowered tumour necrosis factor alpha protein and raised transforming growth factor beta 1, suppressed p38 and c-Jun N-terminal kinase phosphorylation, and blocked nuclear translocation of the NF-kappaB p65 subunit. In a murine excision wound model it lowered tumour necrosis factor alpha and raised transforming growth factor beta 1 in skin and accelerated closure, with thinner epidermis and dermis and less immune cell aggregation on histology [10].

This is the strongest available justification for applying this plant to skin at all, and it establishes that keratinocytes respond to the extract at concentrations that are achievable topically.

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An inconvenient detail about which constituent is responsible

The same study did not chemically characterise the active constituents, and the authors proposed triethylene glycol as a possible active [10]. Triethylene glycol is not a withanolide. Separately, wound-healing activity has been reported for an emulgel of the essential oil fraction of this plant, again not the withanolide fraction [11].

The consequence for formulation is direct and is almost universally overlooked. If the skin activity of W. somnifera is not withanolide-mediated, then standardising the extract to withaferin A, assaying the patch for withaferin A and reporting withaferin A flux measures a marker that may have nothing to do with the effect. The marker would be a tracer of extract loading rather than of activity.

Two things follow. The extraction solvent is not a neutral choice: a hot-water extract, a hydroalcoholic extract and an essential oil fraction of the same root are three different products with three different constituent profiles, and evidence generated with one does not transfer to another. And the marker question should be settled by bioassay-guided fractionation before a formulation programme commits to one, rather than assumed from the plant's general reputation.

THE TRANSDERMAL RATIONALE AND THE PHYSICOCHEMICAL REALITY

The barrier

The stratum corneum is the rate-limiting barrier: fifteen to twenty layers of anucleate corneocytes in an intercellular matrix of ceramides, cholesterol and free fatty acids, conventionally described as bricks in mortar [12]. Permeation is predominantly by the tortuous intercellular lipid route. Beneath it the viable epidermis and vascularised dermis offer little resistance, and a molecule reaching the dermal capillary plexus is removed into the systemic circulation.

Passive transdermal delivery favours molecules below about 500 daltons, of intermediate lipophilicity, with a melting point below roughly 200 degrees Celsius and, decisively, a daily dose of a few milligrams at most [13].

Where withaferin A sits in that window

Withaferin A has the molecular formula C28H38O6 and a molecular weight of approximately 470.6 [14]. That is inside the 500 dalton limit, but at its upper edge, where flux falls steeply with further increase in size. It is a poorly water-soluble steroidal lactone, which helps partitioning into stratum corneum lipids and hinders subsequent partitioning out into the aqueous viable epidermis.

The honest reading is that withaferin A is a borderline transdermal candidate on size, with no particular advantage on solubility, and that the governing constraint is not the molecule but the dose. Section 8 sets out that arithmetic.

What a patch offers, and the comparator it must beat

A transdermal system avoids first-pass metabolism and gastrointestinal exposure, gives a steady input rate rather than peaks and troughs, permits termination by removal, and improves adherence [15]. Matrix patches prepared by solvent casting dominate herbal work because they can be made without specialised equipment.

The comparator, however, is not the oral NSAID. It is the topical NSAID. Diclofenac gels and patches already deliver a defined dose of a defined molecule to a defined site with reduced systemic exposure, and have

been assessed in systematic reviews [16].An ashwagandha patch must be argued against that standard, and in the published literature it almost never is.

PUBLISHED TOPICAL AND TRANSDERMAL FORMULATIONS OF W. SOMNIFERA21 Nov 2026

The plant has been formulated topically more often than the patch literature acknowledges. A transdermal gel of standardised leaf extract has been reported [17]; topical anti-inflammatory gels combining it with Boswellia serrata have been described [18]; a nanoemulgel for osteoarthritis using the same pairing has been reported [19]; and an emulgel of the essential oil fraction has shown wound-healing activity [11].

Two observations follow. First, a matrix patch is not the only, and may not be the best, topical presentation for this plant: a gel or emulgel permits higher extract loading per unit area than a thin cast film, and a nanocarrier addresses the solubility and partitioning problem that a simple film does not. Second, the comparative question has not been asked. No published study appears to compare a patch, a gel and a carrier-based system of the same standardised extract on the same endpoint, which is the comparison that would tell a formulator which presentation is worth developing.

PATCH DESIGN

The polymer

Polyvinyl alcohol is the usual matrix former: it casts readily from aqueous solution, gives a clear flexible film and is inexpensive [20]. The limitation follows from the same property. It is water-soluble, so a hydrophilic film on occluded, hydrating skin will swell and may lose mechanical integrity over a wear period measured in hours. Water uptake values of twenty to thirty per cent, commonly reported as a neutral characterisation, should be read in that light. Blends with a hydrophobic partner such as ethyl cellulose or Eudragit, or crosslinking, are the usual remedies and are seldom explored.

The plasticiser

Polyethylene glycol 400, glycerol and propylene glycol lower the glass transition temperature of the cast film and raise flexibility, reported as folding endurance [21]. Plasticiser level is a genuine formulation variable because it also alters diffusivity within the matrix, and the two effects are rarely separated.

The penetration enhancer

Dimethyl sulfoxide is effective, acting by keratin denaturation and lipid disruption, with a strongly concentration-dependent effect that generally requires high concentrations for substantial enhancement [22,23]. That is also its problem: erythema, stinging and a systemic dimethyl sulfide odour on the breath are recognised, and its acceptability in a chronically worn product is limited. A study that uses it and reports an absence of irritation owes the reader the concentration and the scoring method. Terpenes, fatty acids, oleic acid and propylene glycol are generally preferred for repeated application.

What is usually missing

An adhesive. A matrix film of polyvinyl alcohol with a plasticiser has no pressure-sensitive adhesive layer, and nothing in the standard evaluation battery measures adhesion, peel or tack [24]. In animal work this is concealed by taping the patch in place; in a product it cannot be. A patch that cannot stay on is not a patch.

THE CONVENTIONAL EVALUATION BATTERY

The physical tests

Thickness, weight uniformity, folding endurance, tensile strength, surface pH, moisture content and water uptake are reported almost universally. They are worth doing: they establish that the film is uniform, flexible, mechanically sound and unlikely to irritate on pH grounds.

They establish nothing about delivery. A patch may be perfectly uniform, fold two hundred times and sit at pH 7.4, and release nothing through skin. The weight these tests carry in published discussion is out of proportion to what they measure.

Release testing is not permeation testing

This is the most consequential methodological error in the field. The *in vitro* study is typically run in a Franz

cell with a dialysis or cellophane membrane between donor and receptor, and the result is reported as permeation.

A dialysis membrane is a size-exclusion barrier with no lipid domains, no corneocyte architecture and none of the tortuosity that governs percutaneous absorption. Such an experiment measures release from the matrix, a legitimate quality-control test recognised as such [25,26].It is not absorption, and the guideline governing *in vitro* skin absorption specifies skin [27]. Excised porcine ear skin is the usual practical choice; rodent skin is more permeable than human and flatters the result [28]. A release profile and a permeation profile can differ by an order of magnitude.

The animal models

Carrageenan-induced hind paw oedema and the tail-flick test are the standard pair [29,30]. Two cautions apply with a patch.

The patch is applied to depilated dorsal skin and the oedema is induced in the paw, so any effect requires systemic absorption and distribution. The study therefore tests systemic delivery, not local action. If the rationale is local therapy, the model does not test it; if the rationale is systemic, the arithmetic in Section 8 must be satisfied. Studies frequently assert the first and measure the second.

The tail-flick test is a spinal reflex assay of acute thermal nociception, a reasonable screen for centrally acting analgesia and a poor model of inflammatory pain. For this indication the second phase of the formalin test, or the Randall-Selitto test in a carrageenan-inflamed paw, is more appropriate.

THE ANALYTICAL AND ARITHMETIC PROBLEMS

A single wavelength cannot quantify an extract

Drug content and release are almost always determined by ultraviolet spectrophotometry at one wavelength of maximum absorbance, read against a calibration curve prepared from the same crude extract.

Specificity is the first characteristic required of a validated analytical procedure [31], and this method has none. A hydroalcoholic extract contains hundreds of constituents, many absorbing in the same region. A wavelength near 227 nm, frequently quoted for this plant, lies where essentially every compound bearing a carbonyl or an aromatic ring absorbs, including the polymer, the plasticiser and any degradation product. The number obtained is an absorbance of the extract, not a concentration of anything identified.

The remedy is a marker-based method: a validated high-performance liquid chromatographic or high-performance thin-layer chromatographic assay against withaferin A or withanolide A, with chromatographic fingerprinting for batch consistency [32,33] and the caveat of Section 3.3 about whether that marker tracks activity.

Calibration data deserve scrutiny

Absorbance values above approximately one lie outside the reliable linear range of ultraviolet spectrophotometry, and readings above two are generally stray-light dominated and not meaningful [34]. Peak absorbances in the range of three to four appear in this literature and cannot support a calibration. Calibration tables are also frequently tabulated with volumes in millilitres under a heading of micrograms per millilitre, which leaves the concentration range unstated and the curve uninterpretable.

The payload arithmetic, which is almost never shown

This is the question on which the field turns and the one least often addressed.

Table 1: Illustrative Payload Arithmetic for a Cast Matrix Patch of *W. Somnifera* Extract

Quantity	Illustrative value	Comment
Total patch weight	25-30 mg	As commonly reported for cast matrix patches

Quantity	Illustrative value	Comment
Extract loading	10% w/w	Higher loadings compromise film integrity
Crude extract per patch	2.5-3 mg	-
Declared withanolide content	2.5%	Within the usual commercial range [4]
Total withanolides per patch	60-75 microgram	Total content, before any barrier loss
Fraction crossing skin in 24 h	Typically a small percentage	Unmeasured where a dialysis membrane is used
Withanolide delivered systemically	Sub-microgram to low microgram	To be compared with an effective dose

The figures are illustrative, not measured, and that is the point: the calculation is simple, decisive and almost never presented. Against oral ashwagandha dosed at hundreds of milligrams of extract daily, a patch carrying tens of micrograms of withanolides in total is unlikely to produce a systemic anti-inflammatory effect. Where a paw oedema reduction is nonetheless reported, it requires another explanation, including a vehicle effect from the penetration enhancer itself.

Two honest positions remain. The first is to abandon the systemic claim and pursue local action in skin and underlying tissue, where concentrations can be far higher than in plasma and where, as Section 3.2 shows, keratinocytes demonstrably respond to this extract [10]. That position is well supported for this plant and is the stronger of the two. The second is to raise the delivered dose, by larger area, higher loading, a better enhancer or a vesicular carrier, and to show the arithmetic. What is not defensible is to leave the question unasked.

STANDARDISATION, STABILITY AND THE REGULATORY POSITION

Withanolide content varies with chemotype, plant part, season, geography and extraction solvent, and root and leaf differ materially. Without authentication, a chromatographic fingerprint and a declared marker content, two batches of the same formulation are not the same product [32,33].

In India, Ayurvedic preparations are governed by the Ayurvedic Pharmacopoeia and by the good manufacturing practice provisions for Ayurvedic, Siddha and Unani medicines, while a product presented as a transdermal delivery system raises a classification question that should be settled early rather than at submission [35]. Stability must be conducted under conditions appropriate to the Indian climatic zone rather than temperate-zone conditions [36]; for a patch containing a hygroscopic hydrophilic polymer and oxidisable phenolics, moisture uptake and oxidation are the expected failure modes. A one-month accelerated study, as commonly reported, is a preliminary indication and not a shelf life.

A CRITICAL SUMMARY

Table 2: Recurring Weaknesses and Their Remedies

Weakness	Why it matters	Remedy
Single-wavelength UV assay of a crude extract	No specificity; the figure is not a concentration of anything identified [31]	Marker-based HPLC or HPTLC with fingerprinting
Marker assumed to be a withanolide	Skin activity may not be withanolide-mediated [10,11]	Bioassay-guided fractionation before the marker is fixed
Dialysis membrane reported as permeation	Release is not absorption [27]	Excised porcine ear skin; report deposition and flux separately
Payload arithmetic not shown	The feasibility of the whole approach is unexamined	Calculate delivered marker dose; compare with an effective dose
Extraction solvent treated as interchangeable	Hot-water, hydroalcoholic and volatile fractions are different products [10,11]	State the solvent; do not transfer evidence across extract types
No adhesive, no adhesion testing	A patch that cannot adhere is not a patch [24]	Include and test a pressure-sensitive adhesive

Weakness	Why it matters	Remedy
Enhancer irritation not quantified	DMSO irritation is well recognised [22]	State the concentration; score irritation formally
No active comparator	The relevant alternative is a topical NSAID [16]	Include a marketed topical comparator arm
Patch presentation assumed optimal	Gels and nanocarriers permit higher loading per unit area [17–19]	Compare presentations on one endpoint
Thermal reflex assay used for inflammatory pain	Measures the wrong kind of nociception [29,30]	Use an inflammatory pain model
Extract not standardised	Batches are not equivalent [33]	Declare marker content; fingerprint every batch

WHAT A DEFENSIBLE STUDY WOULD LOOK LIKE

Authenticate the plant material, specify root or leaf, deposit a voucher specimen, and state the extraction solvent as a formulation variable rather than a procedural detail.

Settle the marker question by bioassay-guided fractionation against a skin-relevant endpoint, such as cytokine suppression in keratinocytes, before committing to withaferin A as the analytical marker [10].

Develop and validate a marker-based chromatographic assay in the patch matrix and in skin homogenate before formulation begins [31,32].

Calculate the delivered dose required for the intended effect and design patch area and loading to reach it, stating the assumptions.

Formulate with an adhesive and test adhesion. Use an enhancer whose irritation profile suits repeated wear, and quantify irritation rather than asserting its absence.

Run release across a synthetic membrane as a quality-control test and permeation across excised skin as the delivery measurement, reporting skin deposition alongside flux, since for a locally acting product deposition is the more relevant endpoint [25–28].

Include a blank patch, a marketed topical comparator and, where the claim is that a patch is the right presentation, a gel of the same standardised extract [17].

Use an inflammatory pain model rather than a thermal reflex assay, and measure tissue concentration at the site of action rather than inferring delivery from a distant endpoint [13,14].

Conduct stability under Indian zone conditions for a period that can support a shelf-life claim [36].

CONCLUSION

The premise of a W. somnifera transdermal patch is better supported than that of most herbal patches. The anti-inflammatory mechanism is defined, the plant has been formulated topically in several presentations and, unusually, there is direct evidence that skin cells respond to the extract.

That last point is also where the field should reorient. The strongest case for this plant is not a patch delivering withanolides into the systemic circulation, where the arithmetic is unfavourable; it is a locally acting product producing high concentrations in skin and underlying tissue, where the evidence already exists and where the dose problem largely disappears. Making that case requires abandoning the systemic framing, measuring tissue concentration rather than inferring it, and settling which constituent is actually responsible.

The most useful contribution this field could now make is one study, properly standardised and properly assayed, that states how much of a named marker compound is deposited in skin from a patch of defined area in twenty-four hours, and whether that marker is the one that does the work. Until those two numbers exist, every efficacy claim in the area rests on an unexamined assumption.

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