



**REVIEW ARTICLE**

**Inflammation and Herbal Therapy: A Review**

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**ABSTRACT**

Herbal medicine has become an item of global importance both medicinal and economical. Herbal medicine, also called phytomedicine, refers to using a plant's seed, berries, roots, leaves, bark, or flowers for medicinal purposes. Although usage of these herbal medicines has increased, their quality, safety, and efficiency are serious concerns in industrialized and developing countries. Plant play a vital role in curing various ailments of the man and herbal remedies are getting increasing patient compliance as they are devoid of typical side effects of allopathic medicines. The allopathic system of medicine includes two conventional line of the treatment for rheumatoid arthritis, which comes along with certain side effects. Hence, turning to safe, effective and time tested ayurvedic herbal drug formulation would be a preferable option. So there is need to investigate such drugs and their effective formulation for the better patient acceptance. Considering these facts present review aims to develop herbal anti-inflammatory transdermal patches of a combination of *Sida rhombifolia*, *Alpinia galanga*, and *Tamarindus indica*. Inflammation has become the focus of global scientific research because of its implication in virtually all human and animal diseases. As a result of adverse effects such as gastric lesions caused by non-steroidal anti-inflammatory drugs (NSAID), tolerance and dependence induced by opiates the use of these drugs as anti-inflammatory agents have not been successful in all cases. Therefore, new anti-inflammatory drugs lacking these side effects are being researched as alternatives to NSAIDs and opiates. Attention is being focused on the investigation of the efficacy of plant-based drugs used in the traditional medicine because they are cheap, have little side effects. Hence, in the present review emphasize to produce an outcome which creates an awareness of giving novel drug delivery systems for effective drug delivery for the treatment of inflammation.

**KEYWORDS**

*Sida rhombifolia*, *Alpinia galanga*, *Tamarindus indica*, Inflammation, Gastric lesions, NSAIDs.

**INTRODUCTION**

1. Inflammation

Inflammation is a part of the complex biological response of vascular tissues to harmful stimuli, such as pathogens, damaged cells, or irritants. Inflammation is a protective attempt by the organism to remove the injurious stimuli and to initiate the healing process.

Inflammation is not a synonym for infection, even in cases where inflammation is caused by infection. Although infection is caused by a microorganism, inflammation is one of the responses of the organism to the pathogen. Without inflammation, wounds and infections would never heal. However, chronic inflammation can also lead to a host of diseases, such as hay fever, atherosclerosis, rheumatoid arthritis, and even cancer. It is for that reason that inflammation is normally closely regulated by the body<sup>1</sup>.

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Inflammation is a defense reaction caused by tissue damage or injury, characterized by redness, heat, swelling and pain. The primary objective of inflammation is to localize and eradicate the irritant and repair the surrounding tissue. Inflammation aids disposal of microbes, toxins or foreign material at the site of injury, prevents their spread to other organs and prepares the site for tissue repair. Thus it helps restore tissue homeostasis<sup>2</sup>.

There are three basic stages of inflammation:

- 1) Vasodilatation and increased permeability of blood vessels.
- 2) Phagocyte migration
- 3) Tissue repair

### ***1.1 Signs of inflammation:***

- a) Rubor – redness
- b) Tumor – swelling
- c) Calor – heat
- d) Dolor – pain
- e) Function laesa – loss of function

### ***1.2 Agents causing inflammation:***

- 1) Physical agents: like heat, cold, radiation, mechanical trauma
- 2) Chemical agents: like organic and inorganic poisons
- 3) Infective agents: like bacteria, viruses and their toxins
- 4) Immunological agents: like cell mediated and antibody reaction.

### ***1.3 Types of inflammation:***

#### ***A) Acute inflammation:***

Acute inflammation is of short duration and represents the early body reactions. The main features of acute inflammation are:

- a) Accumulation of fluid and plasma at the affected site,
- b) Intravascular activation of platelets,

- c) Polymorph nuclear neutrophils as inflammatory cells

#### ***B) Chronic inflammation:***

Chronic inflammation is defined as prolonged process in which tissue destruction and inflammation occur at the same site. Chronic inflammation can be caused by-

- a) Chronic inflammation followed by acute inflammation
- b) Recurrent attack of acute inflammation
- c) Chronic inflammation starting de nova

### ***1.4 Treatment of inflammation:***

The inflammation can be treated by;

#### ***a) Nonsteroidal anti-inflammatory drugs***

Like analgesics, non-steroidal anti-inflammatory drugs (NSAIDs) treat pain. Unlike analgesics, these drugs also help prevent painful inflammation and joint damage. They're the top choice for treatment for people with inflammation because they're effective and non-sedating. NSAIDs come in oral and topical forms. There are many different choices, and some are available OTC<sup>6</sup>.

NSAIDs come with risks, even the OTC versions. Side effects can include:

- stomach irritation, erosion, or ulcers (can lead to stomach bleeding and death)
- kidney problems
- If you're allergic to aspirin, you also shouldn't take NSAIDs.

Examples of NSAIDs include:

#### ❖ Aspirin

Aspirin is an OTC NSAID that treats pain and inflammation. It can help treat symptoms to enhance your quality of life.

#### ❖ Ibuprofen (Advil, Motrin, Midol, Nuprin)

Ibuprofen is a NSAID available in both OTC and prescription strengths. Taking ibuprofen long-

term is not recommended because of the risk of stomach bleeding and heart attack.

❖ Naproxen sodium and naproxen (Aleve)

Naproxen sodium is an OTC NSAID. It's used to treat pain and inflammation. Higher doses are also available in prescription forms. This drug has the advantage that it doesn't carry the same risk of heart attack that ibuprofen does.

However, it does have some side effects. These include:

- heartburn
- stomach pain
- nausea
- diarrhoea
- headaches
- dizziness
- drowsiness

❖ *Diclofenac ( Voltaren) and diclofenac-misoprostol (Arthrotec)*

Diclofenac is a prescription NSAID that comes in both oral and topical forms. Diclofenac-misoprostol combines diclofenac with a drug to protect against stomach ulcers. It, too, can cause side effects. These include:

- stomach pain
- diarrhoea
- nausea

**b) Corticosteroids:**

Corticosteroids are also known as steroids. They're sometimes used briefly for severe OA flare-ups. However, they have many risks if they're used for long-term treatment<sup>19</sup>.

Like NSAIDs, steroids reduce inflammation but are hard on the stomach. Unlike NSAIDs, they do not cause kidney problems. This means they may be a safer choice for people with kidney disease.

Steroids are available as oral and injectable forms. The injectable forms are sometimes used for stubborn joints to relieve swelling and pain in that area.

Side effects of all steroids can include:

- high blood sugar levels
- stomach ulcers
- nausea
- diarrhoea
- headaches
- dizziness
- drowsiness

**c) Opioids:**

These prescription pain drugs change the way of feel pain, but they don't prevent inflammation. They're habit-forming and powerful. They can be combined with other treatments that aren't sedating and habit-forming.

Opioids include:

- codeine
- oxycontin
- morphine

**d) Topical analgesics:**

These topical pain drugs come as ointments, gels, or creams. They're alternatives to oral or injectable. They're available over the counter and as prescriptions. Some topical treatments offer immediate, short-term relief. Others offer long-term relief.

Topical analgesics include:

- Capsaicin. Derived from cayenne peppers, this OTC drug comes as an ointment.
- Diclofenac sodium gel and solution (Voltaren, Flector Patch, Solaraze, Pennsaid). This topical NSAID is only available as a prescription.

- Lidocaine patch. This drug can treat a specific area of pain in OA, but it's not usually given as a first treatment.
- Methyl salicylate and menthol (Bengay). This drug cream is made from mint plants and also contains a topical aspirin-like NSAID.
- Trolamine. This topical cream contains an aspirin-like drug that relieves inflammation and pain.

### 3. Plants as natural anti-inflammatory agents

Unlike modern allopathic drugs which are single active components that target one specific pathway, herbal medicines work in a way that depends on an orchestral approach. A plant contains a multitude of different molecules that act synergistically on targeted elements of the complex cellular pathway. Medicinal plants have been a source of a wide variety of biologically active compounds for many centuries and used extensively as crude material or as pure compounds for treating various disease conditions. The use of herbal medicines becoming popular due to toxicity and side-effects of allopathic medicines<sup>4</sup>. Medicinal plants play an important role in the development of potent therapeutic agents. India with its biggest repository of medicinal plants in the world may maintain an important position in the production of raw materials either directly for crude drugs or as the bioactive compounds in the formulation of pharmaceuticals and cosmetics etc

### 2. Plants having anti-inflammatory properties.

S. N	Plant name	Family	Parts used
1	Adhatoda vasica	Acanthaceae	Leaves
2	Aegle marmelos	Rutaceae	Leaves
3	Aloe vera	Asphodelaceae	Leaves
4	Annona squamosa	Annonaceae	Seeds

S. N	Plant name	Family	Parts used
5	Bacopa monnieri	Scrophulariaceae	Whole plant
6	Boswellia serrata	Burseraceae	Resin
7	Cassia fistula	Caesalpinaceae	Leaves
8	Citrus auranticum	Rutaceae	Fruit
9	Commiphora mukul	Burseraceae	Resin
10	Curcuma longa	Zingiberaceae	Rhizomes
11	Embilica officianalis	Euphorbiaceae	Fruit
12	Herera rhombea	Araliaceae	Leaves
13	Lippia germinate	Verbenaceae	Leaves
14	Mangifera indica	Anacardiaceae	Bark
15	Moringa olifera	Moringaceae	Root, Flowers
16	Palisata histula	Commelineaceae	Leaves
17	Phyllanthus polyphyllus	Euphorbiaceae	Whole plant
18	Rubrus ellipticus	Rubiaceae	Leaves
19	Sida rhombifolia	Malvaceae	Root
20	Swertia chirata	Gentianaceae	Aerial part
21	Tamarindus indica	Fabaceae	Leaves
22	Tuberaria lignose	Cistaceae	Leaves

S. N	Plant name	Family	Parts used
23	Vinca rosea	Apocyanaceae	Leaves
24	Xeromphis spina	Compositae	Pulp
25	Zingiber officianalies	Zingiberaceae	Rhizomes

Herbal medicine is also called botanical medicine or phytomedicine -it refers to using a plant's seeds, berries, roots, leaves, bark, or flowers for medicinal purposes. Herbalism has a long tradition of use outside of conventional medicine. It is becoming more useful as improvements in analysis and quality control along with advances in clinical research show the value of herbal medicine in the treating and preventing disease. However, the dependence on synthetics is over and people are returning to the naturals with the hope of safety and security<sup>3</sup>. Herbal medicines have lesser side effects and adverse effects so; they are more and more used for the treatment of various diseases. There are many synthetic drugs for the treatment of inflammation like NSAIDs, Corticosteroids etc, but they have various side effects and adverse drug reactions. So for overcome these adverse effects herbal drugs are incorporated as medicines for inflammatory reactions.

Herbal transdermal drug delivery system is comparatively a newer form of drug delivery system. On the basis of the literature, we selecting *Sida rhombifolia*<sup>5</sup>, *Alpinia galanga*<sup>9</sup>, and *tamarindus indica* <sup>11</sup> are important medicinal plants of many ayurvedic preparations. The anti-inflammatory activity of the both the drugs is well established by many scientific works. The interactions of the ingredients in the process of formulations are unimaginable. Hence, the attempt made in order to assess the concentration of these herbal drugs in the formulation. Very fewer attempts were made to estimate the active constituents in the formulations containing these drugs<sup>5</sup>.

### 3. Controlled drug delivery and Drug targeting.

Various drug delivery and drug targeting system are currently under development to minimize drug degradation and loss, to prevent harmful side effects and to increase drug bioavailability. Controlled drug delivery is a new approach which delivers the drug at a predetermined rate, for locally or systematically for a specific period of time. The main peculiarity of controlled drug delivery system is drug targeting, where the drug has to be encapsulated in carriers. Among drug carriers, one can name soluble polymers, microparticles made of insoluble or biodegradable natural and synthetic polymers, microcapsules, cells, lipoproteins, liposomes, and micelles. Drug targeting is the ability to direct the drug loaded system to the site of interest. Two major mechanisms can be distinguished for addressing the desired sites for drug release:

- (i) Passive targeting
- (ii) Active targeting

The passive targeting utilizes the natural course of bio distribution of the carrier, but in active targeting, it involves the modification or functionalization of the drug carriers<sup>24</sup>.

Potential release mechanism in controlled drug delivery system involves,

- Desorption of surface bound/adsorbed drugs;
- Diffusion through the carrier matrix
- Diffusion (in the case of nanocapsules) through the carrier wall;
- Carrier matrix erosion and
- A combined erosion/diffusion process.

The Sustained (or continuous) release of a drug involves polymers that release the drug at a controlled rate due to diffusion out of the polymer or by degradation of the polymer over time. The pulsatile release is often the preferred method of drug delivery, as it closely mimics the way by which the body naturally produces

hormones such as insulin. It is achieved by using drug-carrying polymers that respond to specific stimuli (e.g. exposure to light, changes in pH or temperature).

#### **4. Herbal novel drug delivery**

In the past few decades, considerable attention has been focused on the development of novel drug delivery system for herbal drugs. Herbal medicines are becoming more popular in the modern world for their application to cure a variety of diseases with less toxic effects and better therapeutic effects. Novel drug delivery system refers to the approaches, formulations, technologies, and systems for transporting a pharmaceutical compound in the body as needed to safely achieve its desired therapeutic effects<sup>23</sup>. Novel herbal drug carriers cure particular disease by targeting exactly the affected zone inside a patient's body and transporting the drug to that area. Novel drug delivery system is advantageous in delivering the herbal drug at predetermined rate and delivery of drug at the site of action which minimizes the toxic effects with an increase in bioavailability of drugs. In novel drug delivery, control of the distribution of the drug is achieved by incorporating the drug in carrier system or changing the structure of the drug at the molecular level.

Incorporation of herbal drugs in the delivery system also aids to increase the solubility, enhanced stability, protection from toxicity, enhanced pharmacological activity, improved tissue macrophage distribution, sustained delivery and protection from physical and chemical degradation.

The herbal novel drug delivery systems have a lot of plus points, several researchers are doing or working towards novel drug delivery systems like mouth dissolving tablets, sustained and extended release formulations, mucoadhesive systems, transdermal dosage forms, micro particles, microcapsules, nanoparticles, implants etc. However, the conventional drug delivery system used for administering the medicine to the

patient is traditional and out-of-date, resulting in reduced efficacy<sup>13</sup>. In the case of herbal extracts, there is a great possibility that many compounds will be destroyed in the highly acidic pH of the stomach while giving orally. Other components might be metabolized by the liver before reaching the blood. As a result, the required amount of the drug may not reach the blood. If the drug does not reach the blood at a minimum level, which is known as 'minimum effective level' then there will be no therapeutic effect. Phytopharmaceuticals are pharmaceuticals using traditional compounds derived from botanicals instead of chemicals. Natural ingredients are more easily and more readily metabolized by the body. Therefore they produce fewer, if any, side effects and provide increased absorption in the bloodstream resulting in more thorough and effective treatments<sup>8</sup>. Pharmaceuticals made from chemical compounds are prone to adverse side effects. The human body will have a tendency to reject certain chemical compounds which do not occur naturally. These rejections occur in the form of side effects; some as mild as minor headaches, and others as severe as to be potentially lethal. It's important to note while phytopharmaceuticals produce fewer to no side effects, chemical interactions with other prescription drugs can occur.

#### **5. Topical novel drug delivery**

Ointments, in general, are composed of fluid hydrocarbons meshed in a matrix of higher melting solid hydrocarbons. They usually contain a medicament or medicaments dissolved, suspended or emulsified in an ointment base (vehicles)<sup>13</sup>.

##### Disadvantages:

- Very greasy
- Stains
- Difficult to wash off
- Contraindicated exudative lesions

##### Creams

Creams are a viscous liquid or semi-solid emulsion of either water- in-oil or oil-in-water. Their consistency and rheologic character depend on whether the emulsion is water in oil or oil-in-water type and/or the nature of the solids in the internal phase. Oil-in-water emulsions are most useful as water-washable bases where as water-in-oil emulsions are emollient and cleansing. Patients often prefer water in oil cream to an ointment because the cream spreads more readily, less greasy and the evaporating water soothes the inflamed tissue.

#### *Disadvantages*

- Stability is not good

#### *Pastes*

Pastes are a mixture of powder and ointment. Like ointments, are intended for external application to the skin. They differ from ointments primarily in that they generally contain a larger percentage of solid material and as a consequence are thicker and stiffer than ointments because of their large percentage of solids. Pastes are generally more absorptive and less greasy than ointments prepared with the same components. Because of stiffness and absorptive qualities of paste, they remain in place after application with little tendency to soften and flow. Therefore these are effectively employed to absorb serous secretions from the site of application.

#### *Disadvantages*

- Less occlusive than ointments
- However, because of their stiffness and impenetrability, pastes are not generally suited for application to a hairy part of the body. Example: zinc-oxide paste

#### *Gels*

Gels are the relatively newer class of dosage forms created by entrapment of large amounts of aqueous or hydro-alcoholic liquid in a network of colloidal solid particles, miscible with water, which may consist of inorganic substances such

as aluminum salts or organic polymers of natural or synthetic origin. Depending upon the nature of colloidal substances and the liquid in the formulation, the gel will range in appearance from entirely clear to opaque. Most topical gels are prepared with organic polymers such as carbomers which impart an aesthetically pleasing, clear sparkling appearance to the product and are easily washed off the skin with water.

#### *Disadvantages*

- Sticky

#### *Lotions*

Application to the skin without rubbing, Cools skin by evaporation of solvents, leaving a thin coat. Dries on the skin soon after application. The most lotion is an aqueous or hydro alcoholic; a small amount of alcohol are added to aid solubilization of the active ingredient and to speed up the evaporation of the solvent from the skin.

#### *Disadvantages*

- Less potent than creams and ointments as they are not as occlusive for long period

#### *Powder:*

Powders are a mixture of finely divided drugs in dry form, which differs from liquid skin care preparation in their physical characteristics. Very fine particle size produces large surface area per unit weight, which covers a large surface area of the body & result in the strong light dispersion. There are body powders, which are also known as a dusting powder or talcum powder, face powder and compact. Medicated powders are used for prickly heat or preventing microbial growth on the skin.

#### *Solution:*

Solutions are liquid preparations of soluble chemicals dissolved in solvents such as water, alcohol, or propylene glycol. Clear in appearance having rapid absorption.

#### *Disadvantages*

- Requires administration of large volume

According to the above discussion, observe that there are various disadvantages for topical dosage form, so tends to select novel controlled drug delivery system for topical administration. Hence the most suitable topical dosage form for anti-inflammatory purpose is transdermal patches.

### 6. Transdermal patches

The most preferred route of administration is the oral route, but oral route have some disadvantages like first pass metabolism, poor bioavailability and tendency to hydrophilic and lipophilic molecules, the capacity of to produce rapid blood level spikes and this leads to prolonging the existence of the drug in the systemic frequent dosing. So to overcome these drawbacks there is a need for the development of new drug delivery system of the capacity of targeting the organs, cells, and tissues. Transdermal drug delivery provides advantages over other formulations<sup>14</sup>. Transdermal drug delivery system [TDDS] is new drugs are easily able to penetrate the skin and easily reach systemic circulation to provide prolonged action of the drug with the target site. TDDS increase the patient compliance and reduces the load as compared to oral route. Transdermal route reduces the side effect caused by oral route<sup>3</sup>. Formulation maintains drug concentration within the Transdermal drug delivery system is an integral part of the therapeutic window for prolong period of time ensuring novel drug delivery system. It is defined as self-contained discrete dosage form that drug levels neither fall below the minimum effective concentration nor exceed the maximum effective concentration which when applied transdermally reaches systemic circulation and controlled release of drugs.

#### *Ideal Characteristics of TDDS:*

- The pH of the solution should be between 5-9.
- For the therapeutic action of the drug, there is a need of optimum partition coefficient. Drugs

with low melting point (less than 200 C) should use.

- Patch size should be less than 40 cm.
- Shelf life up to 2 yrs.

#### *Advantages:*

Transdermal drug delivery systems have some advantages like<sup>23</sup>:

- Increase bioavailability.
- Reduce dosing frequency.
- It is painless and non-invasive drug delivery system.
- Avoid hepatic first pass metabolism.
- Increase patient compliance mainly in pediatric and geriatric patients.
- Maintains stable or constant and controlled blood levels for a longer period of time.
- They provide extended therapy with a single application.
- Self-administration medicament.

### 7. Discussion

On the basis of above discussion, it has been proved that herbal drugs or drugs from the natural origin can be utilized in better form with enhanced efficacy by incorporating them through transdermal route. There are various herbal patches available to lose weight, quit smoking, anti-inflammatory purpose, relieve stress, increase sexuality, as an insect repellent, male energizer, to postpone menopause, which proves the potential of these natural formulations. Thus herbal transdermal patches for inflammation can create wonders in the field of healthcare and is an upcoming area which should be explored further.

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