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REVIEW ARTICLE

Novel Anti-Inflammatory Topical Herbal Gels Containing *Withania somnifera* and *Boswellia serrata*

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ABSTRACT

Herbal medicine has become an item of global importance both medicinal and economical. 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 come along with certain side effects. Hence, turning to safe, effective and time tested ayuvedic 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 novel herbal gel containing the herbs, viz *Withania somnifera* and *Boswellia serrata*. The present study deals that herbal gels formulation of the *Withania somnifera* and *Boswellia serrata* extract using different polymers as the gelling agents and different evaluation parameters provides the effective anti-inflammatory activity to treatment of the inflammation, pain, arthritis etc patients problems. This review focus on the current status of the therapeutic potential and phytochemical profile on the herbal anti –inflammatory agents as *Withania somnifera and Boswellia serrata.* It can also provides the better information regarding to the formulation and evaluation parameters of the novel herbal gel for anti-inflammatory activity and to provide the better therapeutic effects to patient compliance.

Key words: *Withania somnifera, Boswellia serrata*, Herbal gel, Anti-inflammatory activity.

1.INTRODUCTION

During the past decade, the therapeutic use of herbal medicine is gaining considerable momentum in the world. The use of herbal medicine due to toxicity and side effects of allopathic medicines, has led to sudden increase in the number of herbal drug manufactures. Herbal medicines as the major remedy in traditional system of medicine have been used in medical practices since antiquity. The practices continue today because of its biomedical benefits as well as place in cultural beliefs in many parts of world and have made a great contribution towards maintaining human health [1].

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.

There are three basic stages of inflammation:

a) Vasodilatation and increased permeability of blood vessels.
b) Phagocyte migration
c) Tissue repair

- **Signs of inflammation:**

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

- **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

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4) Immunological agents: like cell mediated and antibody reaction.

1.1 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 occurs 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 [2].

Table 1.1 Comparison between acute and chronic inflammation [3]

	Acute	Chronic
Causative agent	Pathogens, injured tissues	Persistent acute inflammation due to non-degradable pathogens, persistent foreign bodies, or autoimmune reactions
Major cells involved	Neutrophils, mononuclear cells (monocytes, macrophages)	Mononuclear cells (monocytes, macrophages, lymphocytes, plasma cells), fibroblasts
Primary mediators	Vasoactive amines, eicosanoids	IFN-γ and other cytokines, growth factors, reactive oxygen species, hydrolytic enzymes
Onset	Immediate	Delayed
Duration	Few days	Up to many months, or years
Outcomes	Resolution, abscess formation, chronic inflammation	Tissue destruction, fibrosis, necrosis

2. Topical Gel Formulations

Topical formulation can be used to manipulate the barrier function of the skin, for example, topical antibiotics and antibacterial help a damaged barrier toward off infection, sun screening agents and the horny layer protect the viable tissues from U.V. radiation and emollient preparations restore pliability to a desiccated horny layer. Direct drugs to the viable skin tissues without using oral, systematic or other routes of therapy. For example, anaesthetic, anti-inflammatory, antipruritic and antihistaminics drugs are to be delivered to viable epidermis and dermis. For skin appendage treatment, for example, antiperspirants, exfolients and depilatories are to be delivered to the skin appendages. Deliver drugs for systematic treatment, for example, transdermal therapeutic systems provide systemic therapy for motion sickness, angina and hypertension.

The U.S.P. defines gels as a semisolid system consisting of dispersion made up of either small inorganic particle or large organic molecule enclosing and interpenetrated by liquid. The inorganic particles form a three-dimensional "house of cards" structure. Gels consist of two-phase system in which inorganic particles are not dissolved but merely dispersed throughout the continuous phase and large organic particles are dissolved in the continuous phase, randomly coiled in the flexible chains.

2.1 Classification of the Gels

Gels are classified mainly by two methods based on:

a) Nature of colloid phase
i) Inorganic gels
ii) Organic gels
b) Based on nature of solvent
i) Aqueous gels
ii) Non aqueous gels

2.2 Gel forming substances

Polymers are used to give the structural network, which is essential for the preparation of gels. Gel forming polymers are classified as follows:

1. Natural polymer

A) Proteins: Collagen, Gelatin

B) Polysaccharides: Agar, Alginate acid, Sodium or Potassium carageenan, Tragacanth, Pectin, Guar Gum, Cassia tora, Xanthan, Gellum Gum

2. Semisynthetic polymers

Cellulose derivatives: Carboxymethyl cellulose, Methylcellulose, Hydroxypropyl cellulose, Hydroxy propyl (methyl cellulose), Hydroxyethyl cellulose.

3. Synthetic polymers

A) Carbomer: Carbopol 940, Carbopol 934
B) Poloxamer
C) Polyacrylamide
D) Polyvinyl alcohol
E) Polyethylene and its co-polymers

4. Inorganic substances

A) Aluminium hydroxide
B) Besitonite

5. Surfactants

A) Cebrotearyl alcohol
B) Brij – 96

2.3 Advantages of Topical gel Formulation

- The topical administration of drug in order to achieve optimal cutaneous and percutaneous drug delivery has recently gain an importance because of various advantages:
- They can avoid gastrointestinal drug absorption difficulties caused by gastrointestinal pH and enzymatic activity and drug interaction with food and drinks.
- They can substitute for oral administration of medication when that route is unsuitable.
- To avoid the first pass effect, that is, the initial pass of drug substance through the
- systemic and portal circulation following gastrointestinal absorption, possibly avoiding
- The deactivation by digestive and liver enzyme.
- They are non-invasive and have patient compliance.
- They are less greasy and can be easily removed from the skin.
- Cost effective.
- Reduction of doses as compare to oral dosage forms.
- Localized effect with minimum side effects.

2.4 Mechanism of Drug Absorption

The rate of permeation across various layers of skin tissues in the course of topical application can be expressed mathematically as

$dQ / dt = Ps (Cd – Cr)$

Where dQ / dt = rate of permeation across various layers.

Cd = concentration of drug in the donar phase.

Cr = concentration of drug in the receptor phase.

Ps = permeability coefficient of the skin tissues.

The concentration in the systemic circulation which is penetrating in the form of pharmacological active form such as :

$Ps = KcDs / hs$

Where Kc = partition coefficient of the penetrant molecules.

hs = overall thickness of the skin tissues.

Ds = apparent diffusivity for the steady state diffusion of penetrate moles.

If Cd >>> Cr than the equation is written as

$dq / dt = PsCd$

2.4.1 Physiological factors in percutaneous absorption

1. Skin integrity
2. Hydration
3. Temperature
4. Anatomic location
5. Age
6. Disease

2.4.2 Formulation factors in percutaneous absorption

1. Occlusivity
2. Drug concentration
3. pH
4. Solubility
5. Surfactant
6. Penetration enhancer

2.5 Methods of Preparation of Gels

- Fusion method
- Cold method
- Dispersion method

2.6 Permeation Enhancer

The skin is a barrier to topically administered drugs. Although the outer layer also provides resistance to the global permeation process, *in-vitro* experiment has shown that the stratum corneum, with 10 – 15 micrometer thickness is the principal barrier. Penetration enhancement technology is a challenging development that would increase significantly the number of drugs available for topical administration. The permeation of drugs through skin can be enhanced by physical methods such as mechanical disruption, electrical disruption, chemical modification and by chemical penetration enhancers e.g. sulphoxides (dimethyl sulphoxides), pyrrolidone, alcohols, glycols, surfactants and terpenes. These compounds increase skin permeability by increasing the partition coefficient of the drug into the skin and by increasing the thermodynamic activity of the drug in the vehicle.

2.7 Evaluation Parameters of the Formulated Gels

- pH
- Drug content
- Viscosity
- Spreadability
- Extrudability study
- Skin irritation studies
- Invitro release
- Invivo study
- Stability

- **Measurement of pH :**

The pH of various gel formulations was determined by using digital pH meter. One gram of gel was dissolved in 100 ml distilled water and stored for two hours. The measurement of pH of each formulation was done in triplicate and average values are calculated.

- **Drug content :**

1 g of the prepared gel was mixed with 100ml of suitable solvent. Aliquots of different concentration were prepared by suitable dilutions after filtering the stock solution and absorbance was measured. Drug content was calculated using the equation, which was obtained by linear regression analysis of calibration curve.

- **Viscosity study :**

The measurement of viscosity of the prepared gel was done with a Brookfield Viscometer. The gels were rotated at 0.3, 0.6 and 1.5 rotations per minute. At each speed, the corresponding dial reading was noted. The viscosity of the gel was obtained by multiplication of the dial reading with factor given in the Brookefield Viscometer catalogues.

- **Spreabability :**

One of the crieteria for a gel to meet the ideal quantities is that it should possess good spreadability. It is the term expressed to denote the extent of area to which gel readily spreads on application to skin or affected part. The therapeutic efficacy of a formulation also depends upon its spreading value. Spreadability is expressed in terms of time in seconds taken by two slides to slip off from gel and placed in between the slides under the direction of certain load.lesser the time taken for separation of two slides, better the spreadability. It is calculated by using the formula:

$$S = M . L / T$$

Where,

- M = wt. tied to upper slide
- L = length of glass slides
- T = time taken to separate the slides

- **Extrudability study :**

The formulations were filled in the collapsible tubes after the gels were set in the container. The extrudability of the formulation was determined in terms of weight in grams required to extrude a 0.5 cm. ribbon of gel in 10 second.

- **Skin irritation study :**

Guinea pigs (400-500 g) of either sex were used for testing of skin irritation. The animals were maintained on standard animal feed and had free access to water. The animals were kept under standard conditions. Hair was shaved from back of guinea pigs and area of 4 $cm.^2$ was marked on both the sides, one side served as control while the other side was test. Gel was applied (500 mg / guinea pig) twice a day for 7 days and the site was observed for any sensitivity and the reaction if any, was graded as 0, 1, 2, 3 for no reaction, slight patchy erythema, slight but cofluent or moderate but patchy erythema and severe erythema with or without edema, respectively.

- ***In vitro* Diffusion studies :**

The diffusion studies of the prepared gels can be carrying out in Franz diffusion cell for studying the dissolution release of gels through a cellophane membrane. Gel sample (0.5g) was taken in cellophane membrane and the diffusion studies were carried out at 37 ± 1° using 250 ml of phosphate buffer (pH 7.4) as the dissolution medium. Five milliliters of each sample was withdrawn periodically at 1, 2, 3, 4, 5, 6, 7 and 8 h and each sample was replaced with equal volume of fresh dissolution medium. Then the samples were analyzed for the drug content by using phosphate buffer as blank.

- ***In vivo* studies :**

Inhibition of carrageenan – induced rat paw odema – Three groups of 6 male wistar albino rats were used one for marketed sample (reference). Other for test formulation and one group for control. The volume of unilateral hind paw test animal were measured. On each paw, 100 mg of preparation was carefully rubbed twice at 1 and 2 h. before carrageenan administration. They were placed in cages with copography meshes. 0.1 ml of 1 % w/v carrageenan was injected subcutaneously into the paw and volume of hind paw measured at hourly interval for 5 h. using a mercury plethysmometer. Percentage of inhibition was calculated.

- **Stability :**

The stability studies were carried out for all the gel formulation by freeze - thaw cycling. In this syneresis was observed by subjecting the product to a temperature of 4° C for 1 month, then at 25°C for 1 month, then at 40°C for 1 month. After this gel is exposed to ambient room temperature and liquid exudates separating is noted[4]

3. Herbal Anti-inflammatory Agents

On the basis of the literature, we selecting *Withania somnifera* and *Boswellia serrata* are important medicinal plants of many ayurvedic preparations. *Withania somnifera* and *Boswellia serrata* are important drugs in many herbal anti-

inflammatory, anti-arthritic formulations. The anti-arthritic activity of the both the drugs are 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 Boswellic acid and Withaferin A in the formulation. Very less attempts were made to estimate the active constituents in the formulations containing these drugs[5].

3.1 *Boswellia serrata (Kunduru)*

Salai guggal is an oleo-gum-resin obtained from *Boswellia serrata* (Family- Burseraceae). It is also known as frankincense in English and Olibanum in arabian. This tree abundantly growing in dry hilly tracts of the India which has been used for variety of the therapeutic purpose such as cancer, inflammation, arthritis, asthma, psoriasis, colitis, crohn's disease and hyperlipidemia. Alcoholic extract of salai guggal was reported to posses anti-inflammatory and anti- arthritic activites in animals which were due to boswllic acids,which are pentacyclic triterpenes.Boswellic acids slectively inhibits leulotriene synthesis by inhibiting 5-LOX in an enzyme directed, non-redox, non-competitive mechanism.

Fig.1: Photographic view of plant *Boswellia serrata*

3.1.1 Botanical Classification

- Kingdom- Plantae.
- Class- Angiosperms
- Subclass- Eudicots
- Order- Sapindales
- Family - Burseraceae
- Genus - *Boswellia*
- Species - *serrata roxb.*

3.1.2 Phytochemical profile of *Boswellia serrata*

Salai guggal contain essential oil, gum and resin .its essential oil is the mixture of monoterpene, diterpenes nad sesquiterpenes. Gum portion of the drug consist of pentose and hexose sugar with some oxidizing and digestive enzymes. Resin portion mainly composed of pentacyclic triterpene acid of which boswellic acid is the active moiety [6].

3.1.3 Dosage-

For inflammatory or asthmatic conditions, 300-400 mg of standardized extract (containing 60% boswellic acids) three times daily is suggested.

3.1.4 Side Effects and Toxicity-

Toxicity studies of Boswellia in rats and primates showed no pathological changes in hematological, biochemical, or hstological parameters at dose up to 1000 mg/kg. The LD_{50} has been established at > 2 gm/kg.

3.1.5 Mechanism of action of the boswellic acid as a anti-inflammatory agent-

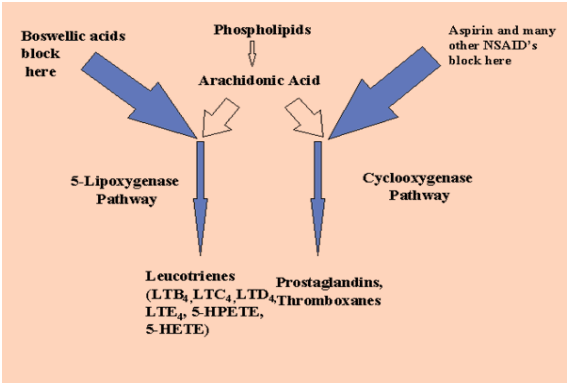

Fig.2: Mechanism of action of Boswellic Acid

Boswellic acid, isolated from the gum of boswellia, in a dose-dependent manner block the systhesis of pro-inflammatory 5- lipoxygenase products. So boswellic acids seem to be specific inhibitors of 5-lipoxygenase[7].

3.2 *Withania somnifera*

Withania somnifera (L.) Dunal is a valued herb, upto 1.5m high shrub with ovate leaves and greenish-yellow flowers can be found in western India, and is locally known as Ashwagandha**.** It has several activities such as anti-inflammatory, muscle weakness and tension, reducing arthritis pain in the knee, rheumatism, anti-diabetes. Withaferin A is a cell-permeable steroidal lactone from a medicinal plant *Withania somnifera* a plant known in traditional Indian medicine. It belongs to the *solanaceae* family. Because it has very less side effect or no side effect; it is also very easily available and cheap as compared to synthetic drugs. It is cost effective, due to easy availability and has higher safety margin.

Fig.3: Photographic view of plant *Withania somnifera*

3.2.1 Botanical Classification

- Kingdom: Plantae.
- Division: Angiospermae.
- Class: Dicotiledoneae.
- Order: Tubiflorae.
- Family: Solanaceae.
- Genus: *Withania.*
- Species: *somnifera* Dunal

3.2.2 Phytochemical profile of *Withania somnifera*

The biologically active chemical constituents are alkaloids (ashwagandhine, cuscohygrine, anahygrine, tropine etc), steroidal compounds, including ergostane type steroidallactones, withaferin A, withanolides Ay, withasomniferin-A, withasomidienone, withasomniferolsA-C, withsomniferin A, withasomnidienone, withasomniferols A-C, withanone etc. The constituents of Withania roots are the steroidal alkaloids and steroidal lactones. They belong to a class of constituents called the withanolides 33, 34, with the main active chemical constituent Withaferin A, a phytosteroid 35. Other constituents include saponins containing an additional acyl group (sitoindoside VII and VIII), and withanoloides with a glucose at carben 27 (sitoindoside ix and x).[8]

3.2.3 Dosage –

A typical dose ashwasgandha is 3-6 grams daily of the dried root, 300-500mg of the extract standardarized to contain 1.5% withanaolides or 6-12 ml of 1:2 fluid extract per day.

3.2.4 Side effects and Toxicity-

Ashwagandha is generally safe when taken in the prescribed dosage range. Large dose have been shown to cause gastrointestinal upset, diarrhea and vomiting.

3.2.5 Warning and contraindications-

Large doses of the ashwagandha may possess abortifacient propertises;therefor it should not be taken during preganancy. Since ashwasgandha acts as the mild central nervous system depressant, patients should avoid alcohol, sedative and other anxiolytics while taking ashwagandha[9].

4. Herbal Anti-inflammatory Gels

Herbal medicines are the synthesis of remedial experiences and practice of indigenous systems of medicine for over hundreds of years. Despite the tremendous progress in medical research during the past decades, the treatment of many serious diseases including pain and inflammation is still problematic. Currently used anti-inflammatory and analgesic drugs are associated with some severe side effects; therefore there is a need for the development of potent analgesic and anti-inflammatory drugs with fewer side effects. Herbal medicine showed safety, efficacy, cultural acceptability and lesser side effects than the synthetic drugs. Natural remedies are more acceptable in the belief that they are safer with fewer side effects than the synthetic ones. So, herbal anti-inflammatory gels which is non-toxic, safe, and effective and improves patient compliance by the utilization of herbal extracts would be highly acceptable.

5. SUMMARY AND CONCLUSION

Different type of topical formulations includes creams, ointments, pastes, gels etc. Out of which gels are getting more popular now a days because they are more stable and also can provide controlled release than other semisolid preparations. The gel formulation of herbal extracts are develops with different gelling agents. The formulative ingredent was carefully selected in consistent with the requirements of a palatable preparation. The gel formulation can provide better absorption characteristics and hence the bioavailability of drug. A thorough investigation into the stability characteristics of the gel formulation over an extended period of time may provide scope for its therapeutic use for patients. For the formulation of the herbal topical gel containing the both of the herbal anti-inflammatory agents extract from the plants. The present review focus on the current state of the therapeutic potential and phytochemical profile on the *Withania somnifera and Boswellia serrata*. It also provides the better information regarding to the formulation and evaluation parameters of the novel herbal gel for anti-inflammatory activity and to provide the better therapeutic effects to patient compliance.

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