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Review

A Comprehensive Review on the Herbal Gels as Effective Topical Therapeutics for Inflammation

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Abstract

Inflammation is a complex response to harmful stimuli and, if uncontrolled, can lead to acute and chronic diseases. While conventional anti-inflammatory treatments like NSAIDs and corticosteroids are effective, they often cause side effects such as skin irritation, systemic toxicity, and impaired wound healing. This has driven interest in safer, natural alternatives like herbal gels. These gels combine bioactive plant compounds with gel-based delivery systems, offering improved skin penetration, localized effects, and better patient compliance. This review explores the phytochemical composition, mechanisms of action, formulation, and pharmacological evaluation of herbal gels for inflammatory conditions. Herbal gels exert anti-inflammatory effects by inhibiting pro-inflammatory enzymes, scavenging free radicals like nitric oxide and reactive oxygen species, and stabilizing cell membranes. Medicinal plants such as Aloe vera, Curcuma longa, Centella asiatica, Boswellia serrata, and Calendula officinalis show promising anti-inflammatory properties in laboratory and some clinical studies. Common pharmacological tests include protein denaturation inhibition and nitric oxide scavenging assays. Despite promising results, challenges remain in standardizing herbal components, ensuring formulation stability, and meeting regulatory requirements. Future progress depends on improved extraction methods, nanoformulations, and clinical trials. With continued research, herbal gels have strong potential as safe and effective alternatives or complements to conventional anti-inflammatory therapies.

Keywords: Herbal gel, Anti-inflammatory, Topical formulation, Phytotherapy, Inflammation management, Medicinal plants, Cyclooxygenase inhibition.

1. INTRODUCTION

Inflammation is an essential defensive response of the body to harmful stimuli, like infections, injuries, or irritants. It is a component of the innate immune system that seeks to eliminate the primary source of cellular

harm, eradicate necrotic cells and tissues, and initiate tissue restoration. Although typically seen negatively due to its relationship with pain and suffering, inflammation is, in fact, a necessary healing process. Dysregulation can lead to tissue damage and chronic illnesses. In recent decades, inflammatory illnesses have risen in prevalence globally, constituting a significant share of morbidity and healthcare costs. Consequently, a primary objective of clinical medicine and pharmacological research is to regulate inflammation efficiently and safely[1].

1.1. Inflammation: Definition and Types

Inflammation can be defined as a localised, defensive tissue response to injury or infection, characterised by the traditional indications of redness (rubor), heat (calor), swelling (tumour), pain (dolour), and loss of function (functio laesa). The response entails the activation of immune cells, the release of pro-inflammatory mediators, vasodilation, heightened vascular permeability, and the migration of leukocytes to the affected region. Inflammation can be categorised into two primary types[2]:

Acute Inflammation

Acute inflammation is a swift and temporary response to tissue injury or microbial invasion, lasting from several hours to days. The increase of neutrophils and other immune cells at the site of injury facilitates pathogen neutralisation and initiates tissue regeneration. Acute inflammation often subsides as the detrimental stressors are removed and homeostasis is restored.

Chronic Inflammation

Chronic inflammation occurs when the inflammatory process persists for an extended duration, ranging from weeks to years. This may result from the failure to eliminate the causative organism, prolonged exposure to low levels of irritants, autoimmune reactions, or persistent infection[3-5]. In contrast to acute inflammation, chronic inflammation is marked by the infiltration of mononuclear cells such as macrophages, lymphocytes, and plasma cells, often resulting in tissue damage and fibrosis. Chronic inflammatory disorders are implicated in numerous diseases, including rheumatoid arthritis, psoriasis, inflammatory bowel disease, cancer, and cardiovascular disease. Controlling inflammation is essential for maintaining tissue function and preventing disease advancement. While pharmacological interventions have demonstrated efficacy, they are not without limitations, particularly for prolonged usage[6].

1.2. Limitations of Conventional Anti-inflammatory Therapies

Pharmacological therapies utilised to manage inflammation mostly include non-steroidal anti-inflammatory medicines (NSAIDs), corticosteroids, and disease-modifying antirheumatic drugs (DMARDs). The mechanism of action is complex, mostly including the inhibition of pro-inflammatory pathways, particularly the cyclooxygenase (COX) enzymes that facilitate prostaglandin formation. Despite their widespread use and efficacy, conventional anti-inflammatory medicines possess some drawbacks[7]:

- **Gastrointestinal Adverse Effects:** Prolonged use of NSAIDs is typically associated with gastrointestinal complications such as gastritis, peptic ulcers, and haemorrhage. This is mostly due to the suppression of COX-1, which plays a protective role in stabilising gastric mucosa.
- **Cardiovascular and Renal Risks:** Selective COX-2 inhibitors, such as celecoxib, were developed to mitigate gastrointestinal adverse effects; nonetheless, they elevated cardiovascular risks. Corticosteroids and NSAIDs may potentially compromise renal function, particularly in those with preexisting kidney conditions[8].
- **Immunosuppression:** Corticosteroids are potent anti-inflammatory agents; but, they can induce immunosuppression, hence heightening patients' vulnerability to infections. Prolonged usage also leads to osteoporosis, adrenal suppression, hyperglycemia, and weight gain.
- **Tolerance and Dependency:** In specific circumstances, extended corticosteroid therapy may result in tolerance or dependency, necessitating cautious tapering to prevent adrenal crisis.
- **Challenges of Topical Formulations:** Topical NSAID medications provide localised relief; nevertheless, their skin permeability is generally limited. Synthetic chemicals in topical formulations may elicit allergic reactions or dermatitis in predisposed individuals.

Due to these limitations, there is increasing interest in safer, natural alternatives that can yield significant anti-inflammatory effects without the systemic side effects associated with synthetic drugs[9].

1.3. Need for Herbal Alternatives in Topical Formulations

Herbal drugs have been in use for thousands of years in traditional healthcare systems like Ayurveda, Traditional Chinese Medicine, and Unani for the control of inflammation as well as inflammation-related disorders[10]. Current pharmacological studies are still affirming the therapeutic value of different medicinal plants and their bioactive compounds in controlling inflammation. Herbal gels, in specific, are a very promising

category of topical drug delivery systems where the benefit of localized drug delivery is fused with the therapeutic benefit of plant-based drugs. The rationale for creating herbal gels for inflammatory conditions such as arthritis is as follows:

- **Localized Action with Lower Systemic Absorption:** Topical herbal gels enable direct application over the inflamed area, maintaining higher local concentrations of active phytoconstituents. Targeted action keeps systemic absorption at a minimum and minimizes systemic side effects, which are typically seen with oral or injectable treatments.
- **Extended Release and Enhanced Permeation:** Formulations of gels with suitable polymers like Carbopol or hydroxypropyl methylcellulose (HPMC) ensure extended release of the drug, thus longer therapeutic effect. Additionally, addition of penetration enhancers or nano-carriers can enhance skin permeation of herbal extracts[11].
- **Synergistic Effects of Phytochemicals:** Several medicinal plants have a range of anti-inflammatory, antioxidant, antimicrobial, and wound-healing actions. Synergistic activity of phytochemicals like flavonoids, alkaloids, and polyphenols effects a combined therapeutic action, which targets several pathways of the inflammatory process.
- **Improved Patient Compliance and Cosmetic Acceptability:** Herbal gels are usually non-greasy, easy to use, and cosmetically acceptable, which improves patient compliance. Unlike ointments or pastes, gels won't stain clothing and are quickly absorbed without leaving a residue behind[12].
- **Cost-Effective and Biocompatible:** Most herbal preparations are cost-effective and biocompatible, with fewer side effects than synthetic preparations. This makes them especially ideal for chronic conditions that need long-term treatment.
- **Formulation Flexibility:** Gels of herbal products can be adapted to meet precise requirements through the choice of appropriate gelling agents, preservatives, and stabilizers. They can also be developed with blends of herbs for multiple therapeutic applications.

The growing popularity of plant-based natural medications, coupled with heightened consumer awareness of the negative effects of synthetic pharmaceuticals, has stimulated significant research and development of herbal anti-inflammatory therapies. Various botanical species, including Aloe vera, Curcuma longa (turmeric), Boswellia serrata, Centella asiatica, and Calendula officinalis, have demonstrated significant anti-inflammatory properties and are commonly utilised in gel-based topical formulations. Despite their potential, herbal gels face challenges that must be addressed, including the standardisation of herbal extracts, inter-batch variability in phytochemical composition, and regulatory concerns[13].

2. Overview of Herbal Gels

2.1. Definition and Benefits of Gel-Based Formulations

Gel formulations are semi-solid substances including active pharmaceutical ingredients (APIs) or bioactive compounds distributed inside an interpenetrating network of hydrophilic or lipophilic polymers. The networks enable the confinement of a liquid within the gel, resulting in a jelly-like consistency[14]. Gels can be categorised as hydrogels (water-in-gel), organogels (oil-in-gel), or emulgels (gel-plus-emulsion), depending on their content and structure. Hydrogels are widely utilised in topical medication delivery due to their ease of application, excellent bioadhesion, and substantial water content. Herbal gels are a specific class of topical gels that incorporate plant-derived active constituents such as extracts, essential oils, or isolated phytochemicals. These gels aim to amalgamate the pharmacological benefits of herbs with the advanced delivery characteristics of gel technologies. The benefits of gel-based formulations are:

- **Application Convenience:** Gels facilitate effortless application on the skin, allowing for more efficient and uniform distribution of the medicine or herbal extract[15].
- **Non-Greasy Consistency:** Unlike ointments and creams, gels include a non-greasy formulation that is more aesthetically pleasing to users, especially for routine or daily application.
- **Enhanced Penetration:** Gels, characterised by their semi-solid nature and aqueous basis, facilitate enhanced penetration of active ingredients through the stratum corneum into the deeper layers of the skin.
- **Cooling Soothing Property:** The elevated water content of hydrogels imparts a soothing quality, rendering them very suitable for inflamed or irritated skin.
- **Extended Release:** Gels can be engineered to administer active drugs by controlled release, thereby maintaining therapeutic levels for an extended period[16].
- **Enhanced Stability:** Sensitive phytoconstituents, such as phenolics and flavonoids, have greater stability in gel matrices compared to solutions or emulsions.
- **Local Targeting:** Topical gels are particularly effective for addressing localised conditions such as inflammation, wounds, arthritis, or skin infections, while minimising systemic side effects.

Due to these benefits, herbal gels have garnered considerable interest in dermatology, pain treatment, wound care, and various other therapeutic domains.

2.2. Advantages of Herbal Gels Over Synthetic Formulations

Herbal gels offer several advantages over synthetic pharmaceutical solutions, particularly in the management of inflammatory conditions. The advantages can be categorised into pharmacological, toxicological, and formulation characteristics.

Natural Origin and Biocompatibility: The herbal gels consist of phytoconstituents sourced from plants, predominantly those that have been traditionally utilised and are generally well tolerated by human skin. Natural origins typically result in enhanced skin compatibility and a diminished incidence of unpleasant reactions such as allergies, dermatitis, or irritation when compared to synthetic substances.

Multifunctional activity: Herbs have a diverse array of pharmacological properties, encompassing anti-inflammatory, antibacterial, antioxidant, and wound-healing effects. Aloe vera possesses anti-inflammatory properties, soothes the skin, and facilitates tissue restoration. These multifunctional activities make herbal gels beneficial in addressing multifactorial illnesses that necessitate many therapeutic interventions[17].

Minimal Adverse Effects: Unlike synthetic corticosteroids or NSAIDs, which may cause skin atrophy, hypersensitivity, or systemic toxicity with prolonged use, herbal gels often exhibit minimal adverse effects when utilised correctly. Consequently, they are optimal for prolonged or chronic applications, such as treating arthritis or eczema. Herbs are generally more sustainable and accessible than synthetic pharmaceuticals. Numerous therapeutic plants can be cultivated or harvested with relatively low environmental impact, and herbal components are generally more affordable, especially in underdeveloped regions.

Patient Acceptance and Compliance: Consumers increasingly prefer natural or organic products over synthetic drugs due to concerns around chemical exposure and drug resistance. Herbal gels align with this trend and typically exhibit greater patient acceptance and adherence.

Synergistic Effects: Numerous herbal formulations contain multiple bioactive compounds that operate synergistically to enhance efficacy. Curcumin in Curcuma longa influences many inflammatory pathways, providing it with a broader therapeutic margin than single-target synthetic compounds.

It is crucial to recognise that while herbal gels offer numerous advantages, challenges such as standardisation, batch-to-batch variability, and regulatory compliance must be addressed by proper formulation and quality control practices[18].

2.3. Common Gel Bases and Excipients in Herbal Formulations

The effectiveness and performance of herbal gels are mostly determined by the kind of gelling agents and other excipients employed. These chemicals regulate the gel's physical features, such as texture and appearance, while also affecting medication release, skin penetration, stability, and patient acceptability.

Gelling Agents: These are the primary structural components that provide the gel its semi-solid consistency. Among the most prevalent gelling agents is Carbopol (Carbomer): A synthetic acrylic acid high-molecular-weight polymer is extensively utilised for its excellent clarity, spreadability, and elevated viscosity at low concentrations. Carbopol gels exhibit pH dependency and require neutralisation, typically with triethanolamine, to achieve stability.

Hydroxypropyl Methylcellulose (HPMC) is a semi-synthetic cellulose derivative that provides a clear, smooth gel basis and is compatible with a majority of herbal extracts. It has moderate viscosity and is non-irritating to the skin. Xanthan Gum: A polysaccharide derived from the bacterium Xanthomonas campestris, xanthan gum is utilised for its stability and elevated viscosity. It is particularly relevant in organic or "green" herbal products. Sodium alginate, derived from brown seaweed, forms hydrogels in the presence of calcium ions. It is utilised in wound-healing gels and various topical herbal preparations. Guar Gum and Locust Bean Gum: Natural, plant-derived gums with thickening properties employed alongside other gelling agents to achieve a thickening effect[19].

Humectants and Emollients: To maintain skin hydrated and prevent dryness:

Glycerin: A widely utilised humectant that draws moisture into the skin.

Sorbitol: An additional humectant, typically utilised in conjunction with glycerin.

Aloe vera gel: Naturally hydrating and soothing, commonly employed as both a foundation and active component.

Preservatives: Employed to suppress microbial proliferation in aqueous formulations:

Methylparaben and Propylparaben - Frequently utilised however contentious concerning potential health effects.

Benzyl alcohol and phenoxyethanol are well-regarded alternatives that have effective antibacterial properties.

Natural preservatives (e.g., grapefruit seed extract, neem oil)- Increasingly favoured in organic herbal formulations.

pH Modulators and Stabilisers: Regarding the formulation's stability and compatibility:

Triethanolamine (TEA)- Utilised as a neutraliser for carbopol and a pH adjuster.

Citric acid or sodium citrate – To maintain the pH within an optimal range (typically pH 5.5–6.5 for skin compatibility).

3. Pathophysiology of Inflammation and Targets for Herbal Gels

Inflammation is a multifaceted biological reaction to detrimental stimuli that can lead to pain, heat, erythema, oedema, or discomfort. The purpose of inflammation is to eliminate the primary source of injury, necrotic cells, and commence tissue restoration. The procedure is stringently regulated and entails a sequence of cellular and molecular occurrences. If unaddressed, inflammation may lead to persistent pathological disorders such as arthritis, psoriasis, and various inflammatory dermatoses. Understanding the pathophysiology of inflammation and the mechanisms by which herbal gels exert therapeutic effects is essential for developing safe and efficient topical treatments[20].

3.1. Molecular and Cellular Mechanisms of Inflammation

The inflammatory response is typically categorised into three phases: start, amplification, and resolution. The initiation phase commences with the identification of danger signals, such as pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), by pattern recognition receptors (PRRs) such Toll-like receptors (TLRs) on immune cells. The detection initiates signalling cascades, particularly the nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) pathways, resulting in the activation of pro-inflammatory genes.

Diverse immune cells are recruited to the wounded site during the amplification process. Neutrophils are the primary cells to arrive and participate in the release of reactive oxygen species (ROS), proteases, and pro-inflammatory cytokines. Macrophages are the second cell type engaged, functioning as effector and regulatory cells, secreting a diverse range of inflammatory mediators that sustain the immune response. The endothelial cells of blood arteries are stimulated and express adhesion molecules such as ICAM-1 and VCAM-1, facilitating the extravasation of immune cells into the tissue.

The resolution phase of inflammation is a dynamic and regulated process. Specialised pro-resolving mediators (SPMs), including as lipoxins, resolvins, and protectins, orchestrate the resolution of inflammation. Macrophages shift from a pro-inflammatory M1 phenotype to an anti-inflammatory M2 phenotype, promoting tissue remodelling and the removal of apoptotic cells.

3.2. Key Inflammatory Mediators: Enzymes and Cytokines

Cyclooxygenase (COX), a pivotal enzyme in inflammation, exists in two isoforms: COX-1 and COX-2. COX-1 is continuously produced and has a role in maintaining physiological functions such as gastric protection and platelet aggregation. COX-2 is, nevertheless, inducible and markedly elevated during inflammation. COX-2 facilitates the transformation of arachidonic acid into pro-inflammatory prostaglandins. Consequently, COX-2 has become a principal target for the development of anti-inflammatory pharmaceuticals. Numerous compounds in herbal gels, such as curcumin from Curcuma longa and boswellic acids from Boswellia serrata, act as natural COX-2 inhibitors by inhibiting prostaglandin-mediated inflammation[21].

Tumour necrosis factor-alpha (TNF-α) is a crucial cytokine in the inflammatory cascade. Primarily secreted by activated macrophages, TNF-α promotes the expression of adhesion molecules on endothelial cells, attracts leukocytes, and stimulates the production of additional pro-inflammatory cytokines, including interleukin-1 (IL-1) and interleukin-6 (IL-6). TNF-α is frequently increased in autoimmune disorders and persistent dermatitis. Herbal extracts from Withania somnifera and Zingiber officinale can inhibit the expression of TNF-α, making them valuable components for anti-inflammatory topical gels.

Interleukins (ILs) have diverse roles in inflammatory processes. IL-1β and IL-6 are potent pro-inflammatory cytokines that provoke fever, increase vascular permeability, and promote leukocyte infiltration. IL-10 is an anti-inflammatory cytokine that suppresses immune responses and promotes healing. The two must be adequately matched to facilitate the resolution of inflammation. Certain herbal constituents equilibrate the two by diminishing IL-1β and IL-6 while augmenting IL-10. Quercetin and flavonoids from Camellia sinensis modulate interleukin levels to facilitate inflammatory regulation.

Nitric oxide (NO), produced by inducible nitric oxide synthase (iNOS), serves as a signalling molecule that facilitates vasodilation and immunological responses. The overproduction of NO, however, induces oxidative stress and exacerbates inflammation. Herbal substances such as flavonoids, catechins, and terpenoids have been shown to decrease iNOS expression and reduce NO production, hence safeguarding tissues against oxidative stress. Green tea polyphenols, particularly EGCG (epigallocatechin gallate), are noted for their inhibitory action on iNOS. The transcription factor NF-κB is a crucial regulator of the inflammatory response. Under resting conditions, NF-κB is sequestered in the cytoplasm by IκB proteins. Activation, through the phosphorylation and degradation of IκB, enables NF-κB to translocate to the nucleus and initiate the transcription of genes encoding inflammatory mediators. Prolonged activation of NF-κB is implicated in chronic inflammation and oncogenesis. Plant-derived substances such as curcumin, resveratrol, and boswellic acids have been extensively studied for their ability to suppress NF-κB activation, hence reducing the expression of pro-inflammatory genes.

3.3. How Topical Herbal Agents Modulate Inflammation

Herbal gels provide bioactive compounds from plants directly to the site of inflammation, achieving a high local concentration with minimal systemic side effects. They provide therapeutic benefits by altering many pathways in the inflammatory cascade and are especially effective for treating localised cutaneous inflammation and musculoskeletal disorders.

The suppression of pro-inflammatory enzymes COX and lipoxygenase (LOX) is a primary mechanism by which herbal gels influence the body. These enzymes facilitate the synthesis of leukotrienes and prostaglandins, which elicit pain, oedema, and erythema. Phytochemicals derived from plants, including curcumin, boswellic acids, and gingerols from Zingiber officinale, inhibit enzymatic activities, hence reducing inflammatory symptoms when applied topically.

Herbal gels also modulate the secretion of pro-inflammatory cytokines. The bioactive compounds of Withania somnifera, Curcuma longa, and Azadirachta indica can inhibit the production of TNF-α, IL-1β, and IL-6. They are generally facilitated by the suppression of transcription factors, such as NF-κB. Herbal compounds can disrupt cytokine synthesis at the genetic level and inhibit the escalation of inflammation and the recruitment of immune cells.

The antioxidant activity is another essential mechanism by which herbal gels mitigate inflammation. Inflammation is initiated by the generation of reactive oxygen species (ROS), which additionally damage tissues and trigger a self-perpetuating cascade of inflammation. Flavonoids, polyphenols, and phyto-vitamins from plants such as Camellia sinensis, Aloe vera, and Ginkgo biloba act as free radical scavengers, neutralising reactive oxygen species (ROS) and reducing oxidative stress in inflamed tissues. The topical application of herbal gels containing antioxidants reduces inflammation and promotes skin regeneration. Topical herbal preparations also regulate the expression and function of transcription factors that govern inflammatory gene expression. Curcumin, resveratrol, and epigallocatechin gallate (EGCG) can inhibit the NF-κB and AP-1 signalling pathways. These effects result in diminished expression of enzymes such as COX-2 and iNOS, decreased cytokine levels, and reduced adhesion molecules, hence offering multi-targeted anti-inflammatory benefits.

In addition to their anti-inflammatory properties, the majority of herbal gels enhance wound healing and skin regeneration. Centella asiatica, Calendula officinalis, and Chamomilla recutita possess chemicals that promote collagen production, fibroblast proliferation, and angiogenesis. These activities are particularly advantageous for treating inflamed skin conditions involving tissue damage, such as eczema, burns, and ulcerations. These herbs, possessing both anti-inflammatory and wound-healing properties, are optimal candidates for incorporation into topical gel formulations.

Moreover, herbal gels often possess antibacterial qualities that combat secondary infections and modulate immune responses. Azadirachta indica (neem), Melaleuca alternifolia (tea tree), and Curcuma longa exhibit extensive antibacterial efficacy against fungus and bacteria. Their presence in gels inhibits microbial invasion and preserves skin hygiene, which is crucial in inflammation-induced wounds and skin diseases. Ultimately, herbal gels support the skin's barrier function by providing hydration, reducing transepidermal water loss, and improving elasticity. Moisturisers such as Aloe vera, glycerin, and natural oils not only mitigate symptoms but also create a conducive environment for the efficacy of anti-inflammatory drugs[22].

4. Herbal Plants with Documented Anti-inflammatory Properties

Herbal medicine has been integral to traditional healing systems worldwide for numerous ages. Numerous plants possess bioactive chemicals with established anti-inflammatory properties, rendering them ideal candidates for the formulation of safe and effective topical gels. These herbs impede their activity via many ways, including the inhibition of inflammatory enzymes, suppression of cytokine production, and scavenging of reactive oxygen species. This is an overview of notable herbal plants extensively studied for their anti-inflammatory properties, particularly in topical applications.

4.1. Aloe vera

Aloe vera, a succulent from the Liliaceae family, is renowned for its calming and therapeutic characteristics. The gel comprises more than 75 active components, including vitamins (A, C, E, B12), enzymes, minerals, polysaccharides, and amino acids. Acemannan, a notable polysaccharide, demonstrates significant anti-inflammatory properties by regulating macrophage function and suppressing pro-inflammatory cytokines, including TNF-α and IL-6[23]. Aloe vera includes enzymes such as bradykinase, which mitigate excessive inflammation when applied externally. Research indicates that Aloe vera gel inhibits cyclooxygenase (COX) activity and reduces prostaglandin E2 (PGE2) synthesis, thereby mitigating inflammation. Aloe vera enhances skin hydration, facilitates epithelial cell migration, and promotes collagen synthesis, rendering it exceptionally advantageous for the treatment of burns, wounds, and many inflammatory skin disorders[24].

4.2. Curcuma longa (Turmeric)

Curcuma longa, often known as turmeric, belongs to the Zingiberaceae family and serves as a fundamental component of Ayurvedic and traditional Chinese medicine[25]. Curcumin is the principal bioactive component of turmeric, a yellow polyphenol, exhibiting a broad range of anti-inflammatory, antioxidant, and antibacterial properties. Curcumin inhibits the action of significant pro-inflammatory mediators, including COX-2, lipoxygenase (LOX), and nuclear factor kappa B (NF-κB). It attenuates the expression of TNF-α, IL-1β, and IL-6, and obstructs the phosphorylation of IκB, so preventing NF-κB translocation to the nucleus. Topical preparations of curcumin have demonstrated significant efficacy in suppressing inflammation, erythema, and oedema in both preclinical and clinical studies. Furthermore, turmeric exhibits significant antioxidant properties that neutralise free radicals and facilitate skin regeneration processes, rendering it an appropriate option for inclusion in anti-inflammatory gels[26].

4.3. Centella asiatica

Centella asiatica, also known as Gotu kola, is a perennial herbaceous plant from the Apiaceae family, prevalent in traditional Asian medicinal practices. Centella asiatica demonstrates its anti-inflammatory properties primarily through its triterpenoid constituents, including asiaticoside, madecassoside, and asiatic acid. These substances suppress the synthesis of inflammatory cytokines, including TNF-α and IL-1β, and mitigate oxidative stress by enhancing the activity of natural antioxidant enzymes, including as superoxide dismutase (SOD) and catalase[27]. Centella asiatica promotes angiogenesis and collagen synthesis, hence aiding in wound healing and tissue restoration. The plant's modulation of fibroblast activity and inhibition of matrix metalloproteinases (MMPs) contribute to its anti-inflammatory and dermoprotective properties. Topical gels containing Centella asiatica extracts are commonly utilised to treat dermatitis, minor burns, and ulcers[28].

4.4. Calendula officinalis

Calendula officinalis, commonly referred to as marigold, belongs to the Asteraceae family and has been utilised since antiquity. The floral extracts are rich in powerful flavonoids, carotenoids, saponins, and triterpenoids, which have significant anti-inflammatory and antioxidant properties[29]. Calendula functions by inhibiting the production of pro-inflammatory prostaglandins and interleukins, and by stabilising lysosomal membranes to prevent the release of inflammatory enzymes. In vitro and in vivo studies have demonstrated that Calendula officinalis mitigates oedema, erythema, and discomfort associated with inflammatory skin disorders. Moreover, it facilitates tissue regeneration, stimulates granulation tissue development, and accelerates epithelialisation, rendering it an optimal choice for topical gels targeting inflammatory and ulcerative dermatological conditions. Its nonirritating properties ensure superior skin tolerance with minimal unwanted effects[30].

4.5. Boswellia serrata

Boswellia serrata, commonly known as Indian frankincense, is a tree indigenous to India and the Middle East, classified within the Burseraceae family, and is known for its production of gum resin that contains boswellic acids. The boswellic acids are the primary bioactive compounds responsible for its anti-inflammatory effects[31]. Boswellic acids specifically inhibit 5-lipoxygenase (5-LOX), an enzyme involved in leukotriene production, hence reducing leukotriene-induced inflammation. Boswellia additionally suppresses the expression of TNF-α and IL-1β, as well as the activation of NF-κB. Clinical investigations have demonstrated the effectiveness of Boswellia extracts in the treatment of inflammatory conditions such as osteoarthritis, rheumatoid arthritis, and inflammatory bowel disease. Boswellia serrata in topical formulations effectively alleviates localised inflammation, discomfort, and oedema. Gels containing boswellic acid are effective for musculoskeletal discomfort, joint inflammation, and inflammatory dermatoses, providing a natural and well-tolerated alternative to synthetic anti-inflammatory medications[32].

4.6. Chamomile (Matricaria chamomilla)

Matricaria chamomilla, also known as German chamomile, is an annual herbaceous plant belonging to the Asteraceae family, traditionally utilised for the treatment of inflammation, spasms, and dermatological conditions[33]. The herb contains various medicinal chemicals, including chamazulene, apigenin, bisabolol, and flavonoids. These contribute to its anti-inflammatory, antioxidant, and antibacterial properties. Chamazulene and bisabolol inhibit the COX-2 and LOX pathways by obstructing the production of prostaglandins and leukotrienes. Apigenin, a flavonoid possessing anti-inflammatory characteristics, functions by inhibiting the NF-κB pathway and modulating the release of pro-inflammatory cytokines. Chamomile exhibits soothing and wound-repairing properties, making it very efficacious in the treatment of eczema, contact dermatitis, and other inflammatory skin conditions. Gels and lotions containing chamomile are frequently utilised in dermatological formulations due to their mild properties and extensive therapeutic applications[34].

4.7. Neem (Azadirachta indica)

Azadirachta indica, also known as neem, is a tree belonging to the Meliaceae family, extensively employed in Ayurveda and Unani medicine for its anti-inflammatory, antifungal, and immunomodulatory properties. The leaves, bark, and seeds of neem contain a variety of bioactive chemicals, such as nimbin, nimbidin, azadirachtin, and quercetin[35]. These substances exhibit anti-inflammatory properties via inhibiting COX and LOX enzymes, suppressing pro-inflammatory cytokines, and modifying the immunological response. Neem demonstrates antibacterial properties against a wide array of microorganisms, preventing subsequent infections in damaged or inflamed skin. Neem's antioxidant properties also mitigate oxidative damage in inflamed tissue. Topical neem gels are widely utilised for the management of acne, eczema, and psoriasis, providing anti-inflammatory advantages and skin protection. Neem is an effective herbal ingredient in polyherbal topical formulations due to its versatility and low toxicity[36].

4.8. Green Tea (Camellia sinensis)

Camellia sinensis, often known as green tea, is a widely eaten beverage plant from the Theaceae family, characterised by its elevated catechin levels, particularly epigallocatechin-3-gallate (EGCG). EGCG has been extensively studied for its antioxidant and anti-inflammatory characteristics[37]. EGCG suppresses COX-2, iNOS, and the production of inflammatory cytokines by blocking the NF-κB and MAPK signalling pathways. EGCG inhibits matrix metalloproteinases (MMPs), which are implicated in tissue breakdown during chronic inflammation. Green tea polyphenols neutralise reactive oxygen species and prevent oxidative cellular damage. Green tea extracts have been effective in dermatological therapies by suppressing UV-induced erythema, acne-related inflammation, and symptoms of atopic dermatitis. Topical treatments made from green tea are valued for their anti-inflammatory effects, anti-seborrhoeic characteristics, and enhancement of skin tone[38].

5. Pharmacological Evaluation of Anti-inflammatory Activity: In Vitro Assays

An evaluation of the anti-inflammatory properties is essential to ascertain the therapeutic efficacy of herbal preparations. In vitro assays provide a rapid, cost-effective, and ethically responsible method for screening herbal extracts and phytochemicals before conducting in vivo investigations. These models replicate fundamental mechanisms associated with inflammation, encompassing protein denaturation, free radical generation, nitric oxide synthesis, and enzyme activity. The following are commonly employed in vitro assays for assessing anti-inflammatory properties, which are beneficial in the preliminary stages of herbal gel development[39].

5.1. Protein Denaturation Assay

Protein denaturation is a fundamental process in inflammation. During inflammation, proteins such as albumin may undergo denaturation due to thermal or chemical influences, leading to the generation of autoantigens that exacerbate inflammatory reactions. The protein denaturation assay quantifies the suppression of protein denaturation by a chemical, serving as an indirect indication of its anti-inflammatory efficacy. In this experiment, a control protein such as bovine serum albumin (BSA) or egg albumin is subjected to heat treatment both with and without the test substance (e.g., herbal extract). The reaction mixture is cooled, and turbidity is measured spectrophotometrically at approximately 660 nm. The decrease in turbidity with the introduction of the test sample indicates the suppression of protein denaturation. The percentage of inhibition is assessed and compared to that of reference anti-inflammatory agents, like diclofenac sodium or aspirin. Herbal extracts rich in polyphenols, including flavonoids and tannins, exhibit significant inhibitory effects in this experiment due to their ability to stabilise protein structures through hydrogen bonding and hydrophobic interactions. The protein denaturation assay is straightforward, reproducible, and provides an early indication of the protective effects of phytochemicals against inflammatory damage[40].

5.2. Nitric Oxide (NO) Scavenging Assay

Nitric oxide (NO) is a crucial mediator of inflammation produced in excess by inducible nitric oxide synthase (iNOS) during immunological activation. While nitric oxide (NO) plays a role in host defence, its overproduction can result in oxidative stress, vasodilation, and tissue damage, hence exacerbating inflammatory responses. The nitric oxide scavenging assay evaluates the ability of herbal extracts to neutralise nitric oxide, hence demonstrating their effectiveness in mitigating nitric oxide-mediated inflammatory responses. This assay relies on the generation of nitric oxide by sodium nitroprusside in an aqueous solution at physiological pH. NO interacts with oxygen to generate nitrite ions, which can be identified using the Griess reagent. The Griess reaction involving nitrites and the Griess reagent yields a pink azo dye, with absorbance measured at 540 nm. The presence of a test sample without scavenging action results in a diminished nitrite concentration, leading to a fall in absorbance. Plant compounds such as flavonoids, phenolic acids, and alkaloids can neutralise nitric oxide radicals by transferring hydrogen atoms or electrons, so interrupting the oxidative reaction chain. The NO

scavenging assay effectively identifies antioxidant-based anti-inflammatory compounds in herbal extracts and correlates antioxidant capacity with anti-inflammatory effectiveness[41].

5.3. Human Red Blood Cell (HRBC) Membrane Stabilization Assay

The HRBC membrane stabilisation test is based on the premise that erythrocyte membranes resemble lysosomal membranes, which are targets of inflammation. Upon release during inflammation, lysosomal enzymes synergistically contribute to tissue damage and the creation of inflammatory signals. Membrane stabilisers that prevent lysis can serve as protective and anti-inflammatory agents.

In this assay, human erythrocytes are isolated and suspended in an isotonic buffer solution. The test sample is integrated, and the suspension is exposed to heat or hypotonic conditions to induce haemolysis. The release of haemoglobin from lysed erythrocytes is quantified by measuring absorbance at 540 nm. A lower absorbance result indicates a more significant membrane stabilisation effect of the test substance[42].

Plant substances with anti-inflammatory properties typically stabilise biological membranes by interacting with membrane proteins and lipids, thereby preventing their degradation. Herbal extracts such as Aloe vera, Centella asiatica, and Azadirachta indica shown significant membrane-stabilizing properties, validating their use in topical gels for inflammation and skin irritation.

5.4. Cyclooxygenase (COX) Inhibition Assay

Cyclooxygenase (COX) enzymes are crucial in the inflammatory response, facilitating the conversion of arachidonic acid into prostaglandins that elicit pain, fever, and oedema. Two isoforms exist: constitutive COX-1 and inducible COX-2, the latter associated with inflammation. The selective inhibition of COX-2 presents a favourable treatment alternative due to its reduced gastrointestinal adverse effects[43].

The in vitro COX inhibition experiments necessitate the incubation of the enzyme with the test sample and arachidonic acid. The quantification of prostaglandin production is achieved by spectrophotometry, enzyme-linked immunosorbent assay (ELISA), or fluorescence-based techniques. The extent of inhibition reflects the enzyme's ability to suppress inflammatory prostaglandin production.

Phytochemicals such as curcumin (Curcuma longa), boswellic acids (Boswellia serrata), and gingerols (Zingiber officinale) have demonstrated specific inhibition of COX-2 in vitro. COX inhibition assays are crucial for evaluating the mechanism of action of herbal gels designed to locally mitigate pain and inflammation.

5.5. Lipoxygenase (LOX) Inhibition Assay

The LOX enzymes facilitate the oxidation of polyunsaturated fatty acids into leukotrienes, which are involved in bronchoconstriction, vascular permeability, and the recruitment of inflammatory cells. Inhibiting the activity of LOX is an additional emphasis for anti-inflammatory medicines. The LOX inhibition assay typically utilises soybean LOX or human recombinant LOX enzymes. The generation of hydroperoxides from arachidonic acid or linoleic acid is monitored spectrophotometrically at 234 nm. The test sample is incubated with the substrate and enzyme, and the reduction in product production indicates LOX inhibition. Herbal substances such as baicalein, catechins, and resveratrol are documented as LOX inhibitors. This assay is useful for inhibiting leukotriene-mediated inflammation, such as in asthma or allergic dermatitis. Integrating these bioactives into a herbal gel may enhance its medicinal efficacy.

5.6. Reactive Oxygen Species (ROS) Scavenging Assays

Inflammation frequently coexists with oxidative stress resulting from the excessive generation of reactive oxygen species (ROS), such as superoxide, hydrogen peroxide, and hydroxyl radicals. These compounds compromise cellular integrity, exacerbate inflammatory reactions, and impede recovery. Consequently, antioxidant assays serve as indirect indicators of anti-inflammatory effectiveness by assessing a compound's efficacy in scavenging reactive oxygen species (ROS). Commonly used ROS assays include:

- DPPH radical scavenging assay-Evaluation of the ability to neutralise DPPH radicals (change from deep violet to colourless).
- ABTS assay -Evaluates the ability to neutralise ABTS•+ radicals.
- Superoxide scavenging assay-Assesses the suppression of superoxide generation.
- Hydroxyl radical scavenging assay - Evaluates the neutralisation of hydroxyl radicals through the breakdown of deoxyribose.

Numerous herbal extracts, including green tea, turmeric, and neem, exhibit substantial antioxidant activity in assays that correlates with their anti-inflammatory properties. The use of antioxidants in topical formulations protects tissues against reactive oxygen species-induced damage during inflammation[44].

6. Challenges and Future prospects

Despite the growing popularity and scientific validation of herbal gels for inflammatory illnesses, several difficulties hinder their broader clinical acceptability and commercialisation. These encompass

formulation issues, standardisation challenges, regulatory obstacles, and insufficient scientific proof. Nonetheless, research initiatives and technological advancements offer promising prospects to surmount these constraints and enhance the use of herbal gels in modern medicine. A primary challenge in developing herbal gels is the standardisation and homogeneity of herbal raw materials. The concentration of bioactive constituents in plant materials varies according to species, geographical region, harvesting season, and extraction procedures. The variability can significantly impact the repeatability and therapeutic efficacy of the final product. Batch-to-batch consistency is achieved by rigorous standardisation protocols, genuine botanical materials, and advanced analytical techniques such as HPLC, GC-MS, and spectrophotometry. The second major obstacle is the stability of the formulation. Many herbal compounds exhibit restricted water solubility, sensitivity to light, oxidative instability, or susceptibility to microbial degradation, all of which might affect the product's shelf life and efficacy. The development of stable products with prolonged biological efficacy is essential. The application of biocompatible gelling agents, preservatives, and encapsulating technologies (such as liposomes and nanoemulsions) can improve the stability, permeability, and targeted administration of phytoconstituents. The absence of clinical proof further limits the application of herbal gels in a medical context. Despite several in vitro and in vivo research indicating potential anti-inflammatory effects, there is a scarcity of well-designed large-scale human clinical trials. The lack of adequate toxicological and pharmacokinetic evidence for numerous herbal preparations poses a challenge for regulatory approval. Robust clinical trials are necessary to validate efficacy, safety, and dosing guidelines for topical herbal formulations.

Regulatory frameworks present further obstacles. Herbal goods are subject to diverse regulations between countries, akin to cosmetics, traditional medicines, or over-the-counter drugs, leading to inconsistent quality control and clearance requirements. Standardised and streamlined rules for herbal topical treatments could facilitate their global market entry and bolster consumer confidence. Notwithstanding these challenges, the future of herbal anti-inflammatory gels is promising. Phytochemical extraction, biotechnology, and medication delivery systems are creating novel pathways for enhanced and reliable formulations. Techniques such as supercritical fluid extraction and the use of green solvents yield superior recoveries of bioactives with reduced degradation. Innovative delivery technologies, including hydrogels, nanogels, and transdermal patches, enhance skin penetration, bioavailability, and the sustained release of herbal pharmaceuticals. The increasing demand for natural, ecological, and chemical-free healthcare alternatives is driving consumer and commercial interest in herbal therapies. Integrating traditional knowledge with modern pharmaceutical sciences may accelerate the creation of standardised, effective, and user-friendly herbal gels. In conclusion, although the persistent formulation hurdles, standardisation issues, regulatory concerns, and clinical validation, the prospects for herbal gels in anti-inflammatory treatment appear bright. Through ongoing research endeavours, interdisciplinary collaboration, and regulatory advancements, herbal gels are set to become prevalent therapeutic agents for addressing inflammatory skin and musculoskeletal conditions.

7. CONCLUSION

The management of inflammation, particularly through topical methods, remains a crucial area in both modern and traditional healthcare systems. Inflammation, although a crucial defensive mechanism, can become pathological when it is chronic or excessive, leading to pain, tissue damage, and exacerbation of various dermatological and musculoskeletal disorders. Synthetic anti-inflammatory medications, including NSAIDs and corticosteroids, are typically preferred treatments; nevertheless, prolonged usage often results in significant side effects such as dermal atrophy, delayed wound healing, and systemic toxicity. This has further invigorated the pursuit of safer and more biocompatible alternatives, particularly from natural sources.

Herbal gels have emerged as a potential solution to this issue. Gels, as semi-solid dosage forms, offer numerous advantages including user-friendliness, enhanced patient adherence, improved skin permeation, and targeted action with diminished systemic absorption. Formulated with anti-inflammatory herbs, gels provide a synergistic therapeutic effect by combining the healing and calming effects of herbal extracts with the advantageous physical attributes of gels. Herbal gels may include many phytoconstituents that operate through diverse pathways, offering multi-targeted and broad-spectrum efficacy against inflammation. Numerous therapeutic herbs, including Aloe vera, Curcuma longa, Centella asiatica, Boswellia serrata, Calendula officinalis, Neem, and Green Tea, have demonstrated significant anti-inflammatory effects via established molecular mechanisms. This encompasses COX inhibition, LOX and NOS pathway inhibition, and suppression of cytokines TNF-α and interleukin. In vitro experiments such as protein denaturation, nitric oxide scavenging, and membrane stabilisation have effectively demonstrated the anti-inflammatory properties of these plants. This information not only substantiates the historical use of these plants but also facilitates evidence-based product creation. The shift of herbal gels from traditional remedies to scientifically validated medicinal solutions faces numerous hurdles. Challenges related to standardisation, stability, formulation optimisation, and regulatory approval must be systematically addressed. The inconsistency in the quality of plant materials, variability in extraction methods, and insufficient clinical trials frequently undermine the reliability and acceptance of herbal

gels in mainstream medicine. Moreover, the absence of standardised regulatory frameworks complicates worldwide commercialisation.

Future advancements in drug transport science, phytochemical characterisation, and formulation technology hold significant potential for overcoming these obstacles. Innovative technologies such as nanogels, transdermal systems, and smart hydrogels can significantly improve the efficacy and usability of herbal anti-inflammatory treatments. Interdisciplinary collaboration among pharmacologists, botanists, formulation scientists, and regulatory scientists is crucial for translating traditional herbal knowledge into clinically viable and commercially effective anti-inflammatory topical treatments. In conclusion, herbal gels represent a secure, efficacious, and sustainable alternative for the treatment of inflammatory illnesses. Their worldwide efficacy, little adverse effects, and alignment with consumer preferences for natural treatments render them very suitable for modern dermatological and therapeutic applications. Through continuous research, rigorous validation, and improved regulatory clarity, herbal gels can substantially advance the future of integrative and evidence-based medicine.

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