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Review Paper

A Review on Herbal Pain Relief Gels: Formulation and Therapeutic Potential of Nirgundi, Boswellia, and Ashwagandha

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ABSTRACT

The application of herbal therapeutics in managing pain has been declared to attain more and more attention because of the multi-target effects and good safety profiles of herbal therapeutics. Three notable medicinal plants are used in the treatment of musculoskeletal pain and inflammation and they include Nirgundi (*Vitex negundo*), Boswellia (*Boswellia serrata*) and Ashwagandha (*Withania somnifera*). Each of them has its own phytochemicals but when combined they act synergistically. The phytoconstituents, mechanisms of action, and therapeutic evidence are summarized and recent improvements in topical gel formulations to promote skin permeation and local analgesic effects are discussed. Nirgundi has anti-inflammatory and antioxidant effects by regulating the production of prostaglandins and free radicals; Boswellia has a significant effect of inhibiting the production of 5-lipoxygenase and leukotrienes; Ashwagandha has an adaptogenic, anti-inflammatory, and neuromodulatory effect via withanolides. Recent studies of formulation show that with the use of appropriate gelling agents, permeation enhancers and stabilizers, optimised gels and emulgels can greatly enhance drug release, spreadability, and patient acceptability. In general, the Nirgundi, Boswellia and Ashwagandha gel system offers a plausible natural intervention to treat musculoskeletal pain and additional standardized clinical studies and refinement of the formulations need to be conducted to better define the therapeutic potential of the mentioned combinations.

INTRODUCTION

Overview of joint disorders:

Joint pain is common and often disabling health problem that effects many people around the world. It can lead to major difficulties in movement

and a noticeable decline in overall quality of life. This condition can arise from several causes, but osteoarthritis (OA) and rheumatoid arthritis (RA) are the two most common types of arthritis linked to joint pain. Among these, OA is especially limiting because it involves the slow breakdown of

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cartilage -the smooth, cushioning tissue that protects the ends of bones within a joint. As this cartilage wears away, the bones begin to rub against each other, causing pain, stiffness, and reduced mobility[1]. Arthritis is an autoimmune disorder that affects around 0.5-1% of people worldwide. Commonly prescribed drug for rheumatoid anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs (DMARDs), and immunosuppressants. However, these medications can cause side effects such as gastrointestinal problem, weakened immunity, and Ayurveda, are increasingly being recognized as alternative approaches for managing arthritis.[2] Rheumatoid arthritis (RA) is a long-term inflammatory disease that does not only affect the joints but can also involve other organs such as the heart, lung, kidney, digestive system, skin, eyes, and nervous system. It occurs in about 1-3% of the population, and women are affected more often than men, especially at younger ages. Research suggests that genetics may play a role in its development. RA causes continuous damage to the joints lined with synovial tissue, leading to pain, stiffness, deformity, and loss of movements, and tendonitis is associated with it as a key feature of this disease. Although rheumatoid arthritis has no permanent cure, different treatments are available to reduce symptoms and improve quality of life. These include medication that control inflammation, physical therapy to improve strength and mobility, and therapeutic injections. However, many medications can cause serious side effects and are often expensive. The most commonly prescribed drug groups are non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and disease-modifying antirheumatic drugs (DMARDs). NSAIDs and corticosteroids usually act quickly, while DMARDs may require several weeks or months to show benefits. Because of these limitations, researchers are exploring safer alternative

approaches. Recent studies have investigated the development of topical herbal gels using natural ingredients such as ginger, garlic, clove, and eucalyptus for managing joint pain and inflammation. However, several factors must be considered when creating topical formulations. The properties of the skin can vary widely from person to person, influencing how well a drug is absorbed. Since the outer layer of the skin (the stratum corneum) acts as a protective barrier, the therapeutic effect of a topical product depends on how much and how deeply the active ingredients can penetrate. Topical medication must be safe, should not contain highly sensitizing substances, and should be formulated to allow proper absorption and dosage needs, especially when products designed for adults are used for children. To enhance drug delivery through the skin, physical techniques such as ultrasound (phonophoresis) and electrical stimulation (iontophoresis) are sometimes used. These methods help increase the permeability of the skin and transport medications more efficiently although more research is needed to confirm long-term treatment benefits [3]. The International Association for the Study of Pain defines pain as a multidimensional entity that involves nociception, afferents to the central nervous system, modulation, affective responses, endogenous analgesia, behavioral adjustments, and changes of social roles. While pain trigger factors are endured, pain degenerates to an independent response, manifesting even when it is possible to eradicate the primary stimulus. Despite technological advances and thorough established treatments, chronic pain continues to defy health professionals, because it is a poorly controlled condition partly because there are three aspects involved in the pathogenesis of pain: nociception (pain sensation and topography), emotional (fear and depression), and behavioral factors (catastrophism, vigilance, and somatic awareness).



Pain management faces difficulties that restrict therapeutic success, such as the limited efficiency of analgesics, systemic effects, and cognitive impairment of drugs due to central effects. As the understanding of pain pathophysiology and treatment increases, new routes of drug delivery are being discovered with the objective of attempting to block pain at peripheral sites, with maximum active drug and minimal systemic effects. Topical preparations are the result of such exploration. For patients, the rationale is the application of analgesics directly on the site of soreness, even if the sensation is a referred pain from another source. They perceive that oral treatments can potentially lead to more adverse effects as compared to topical treatment. In addition, the intention of applying localized treatment within the lay population may be a means of enhancing the efficacy of the placebo element of topical analgesia. Such mechanisms are of limited value if the area of soreness is large, such as an entire limb in sympathetically maintained pain syndromes, and overall, placebo interventions do not seem to be involved in important clinical effects. Nevertheless, it is well known that placebo interventions may influence reported outcomes, especially pain, nausea, and other subjective complaints that are subject to context[4].

Benefits of topical delivery:

Herbal therapies are more likely to be used by those with a better education, poorer health status, and a holistic orientation to health; those wanting relief from symptoms or seeking improvement in their general condition; and those who had a transformational experience that changed their world view. The most commonly used natural products are echinacea, ginseng, ginkgo biloba, and garlic supplements.

Common Herbal Ingredients in Pain Relief Gels:

Among the most widely known drugs with peripheral effects are nonsteroidal anti-inflammatory drugs (NSAIDs), anesthetics, capsaicin, alpha-adrenoreceptor antagonists, and cannabinoids. However, not all medications applied topically on the skin have peripheral action. Topically applied opioids predominantly have a central effect. Therefore, one can didactically distinguish transdermal medication such as buprenorphine and fentanyl and topical drugs acting locally, which have a primary role on the peripheral nervous system and decrease of nociceptive afferents. Several adjuvants such as viscosity and permeation enhancers, emollients, and preservatives are added to the active component, with the objective of reducing the drug concentration, increasing the absorption, maintaining the drug at the target site, and warranting less toxicity, less clearance, and greater analgesic effect. Topical preparations are believed to avoid issues associated with oral or intravenous routes such as gastric disturbances, first-pass hepatic metabolism, and variable serum concentrations. In addition, systemic absorption can be reduced without compromising the desired effect.

However, several items must be considered regarding topical preparations. Marked interindividual variability of skin properties may influence percutaneous absorption and distribution of the drug when applied topically, since the stratum corneum is a barrier that limits penetration of substances. The therapeutic effects also depend on the rate, amount, and depth of penetration into the skin and the potential toxicological hazards of drugs. High doses of sensitizing molecules cannot be administered or diffused into skin, and topical preparations should be water soluble and have an affinity for lipids. Besides, the amount of



variability of individual metabolic properties directly influences bioavailability and needed doses or precautions. This is of special interest when a well-established preparation used in an adult population is used for children in an off-label or unlicensed fashion[4]. Neuropathic pain can have a significant effect on mood and quality of life. This impact can be measured using the Pain detect Questionnaire, the Pain Disability Index, the Beck Depression Inventory the Depression, Anxiety and Stress Test, the Hospital Anxiety and Depression Scale, and the Profile of Mood States (POMS). These questionnaires can be completed at an initial consult to detect if such an impact is present, and thereafter, a more formal assessment can be done by the allied health professional team. The psychologist plays an important role in quantifying the degree of catastrophizing, impact on mood and quality of life, coping strategies, and kinesophobia. This is typically performed utilizing a range of validated scales that include the Pain Catastrophizing Scale Pain Coping Inventory, and the Tampa Scale of Kinesiophobia The Brief Pain Inventory is used to assess condition-specific quality of life (QOL), and the EQ-5D or SF-36 assess overall health-related QOL.[5]

A MEDLINE/PubMed search, covering the period from inception through August 2011, was conducted using the keywords topical analgesic AND chronic pain OR acute pain OR neuropathic pain. The keyword postoperative pain was not included in the search, which largely restricted the search to acute pain conditions other than postoperative pain. In addition, the search was restricted to English-language articles describing individual clinical trials (not reviews of published clinical trials) in humans Topical formulations of a variety of analgesics have been studied for the treatment of diverse indications (Supplemental Table). However, many of the published studies were small, and studies involving patients with

chronic pain were often of short duration. NSAIDs are among the most commonly prescribed drugs throughout the world,124 and hence, it is not surprising that topical formulations of these agents have been studied more widely than topical formulations of other agents.[6]

Plant Materials

The apple cultivar 'Paprastasis antaninis' was used in this study. The apple trees were grown in the experimental orchard of the Institute of Horticulture, Lithuanian Research Centre for Agriculture and Forestry, Babtai, Lithuania (55°60' N, 23°48' E). The altitude of Babtai town is 57 m above sea level. The apples, harvested in September 2020, were immediately lyophilized and used for the study. All solvents, reagents, and standards used were of analytical grade. The standards used in the HPLC analysis were the following: hyperoside, rutin, quercitrin, phloridzin, procyanidin B1, procyanidin B2 and chlorogenic acid, obtained from Extrasynthese (Genay, France); reynoutrin, (+)-catechin and (–)-epicatechin, purchased from Sigma-Aldrich GmbH (Buchs, Switzerland); and avicularin and isoquercitrin, obtained from Chromadex (Santa Ana, CA, USA). The chemicals applied in the modeling of semi-solid pharmaceutical forms were glycerin, castor oil, sorbitan monolaurate (Span 20), polyethylene glycol sorbitan monolaurate (Tween 20) and sodium hydroxide (NaOH), obtained from Sigma-Aldrich Chemie GmbH (Steinheim, Germany). Carbomer 980 was obtained from Lubrizol (Wickliffe, OH, USA). The reagents used in the antioxidant activity assay were 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (Trolox), 2,2-diphenyl-1-picrylhydrazyl (DPPH) and sodium acetate, acquired from Scharlau (Barcelona, Spain). Iron (III) chloride hexahydrate ($\text{FeCl}_3 \times 6\text{H}_2\text{O}$) was purchased from Vaseline-Fabrik Rhenania (Bonn, Germany) and 2,4,6-tri(2-pyridyl)-s-triazine



(TPTZ) was obtained from Carl Roth (Karlsruhe, Germany).

Preparation of the Apple Lyophilizate

The apples were cut into slices of equal size (up to 1 cm in thickness), and the stalks and the seeds were removed. The apple slices with peel were immediately frozen in a freezer (at -35°C) with air circulation. The apple samples were lyophilized with a ZIRBUS sublimator $3 \times 4 \times 5/20$ (ZIRBUS technology, Bad Grund, Germany) at a pressure of 0.01 mbar (condenser temperature, -85°C).

Formulation Strategies:

The leaves of *Vitex negundo* and *Cardiospermum halicacabum* were processed to remove earthy matter and residual materials carefully from the leaves, then cleaned and shade dried. Coarse powdered leaves of *Cardiospermum halicacabum* was extracted in a Soxhlet extractor with methanol for 72 h. Coarse powdered leaves of *Vitex negundo* was extracted with methanol by cold maceration process for 7 days. Both the extracts were then filtered and concentrated under reduced pressure in IKA Rotary evaporator (Model No RN 10 digital V, ILMAC Germany) at 40°C and stored at $4-8^{\circ}\text{C}$ for further use. Carbopol 934 was dissolved slowly with stirring in 60 mL of demineralized water for 1 h to avoid agglomeration. Then disodium edetate and triethanolamine were dissolved in 10 mL of demineralized water separately and stirred for 10 min. Mixed 4.83 mL of propylene glycol in 12 mL of demineralized water with stirring for 10 min. Disodium edetate and triethanolamine solution were added to carbopol solution and the pH was then adjusted to 7.4 by stirring the solution for 10 min. Then propylene glycol solution was added with stirring for 10 min until a clear consistent gel base was obtained.[2] ISOLATION OF

PIPARINE: 150mL of 95% ethanol and 5 boiling chips was added in 15g black pepper and heat at reflux for 2hrs. Using suction filtration, the mixture was filtered and then concentrated to a volume of 10-15mL by simple distillation. 10mL of 10% solution of KOH in 95% ethanol was added in a 125mL Erlenmeyer flask and concentrated pepper extract was mixed and heated. The resulting mixture was diluted with water. A yellow precipitate was formed. Water was added to yellow precipitate until no more solid appears and then the mixture was allowed to stand at least overnight. The resulted solid extracts were collected by suction filtration and recrystallized with 10-20mL of acetone. Gel with Carbopol base: Propylene glycol was heated at 65°C then methyl paraben and propyl paraben was added along with water and carbopol, and kept for 8 hours for adequate swelling of polymer. Triethanolamine was added to neutralize the carbopol and pH was adjusted to 6.7 – 6.9. Propylene glycol at 65°C was heated in another vessel, and drug aceclofenac was added. The above mixture was allowed to cool at room temperature and carbopol base was added. Menthol was dissolved in IPA till the clear solution was obtained; this solution was added to above gel. Oil phase was prepared by dissolving tween 60, chremophore Rh 40, methyl salicylate, linseed oil and peparine together, oil phase was slowly added in the above aqueous carbopol gel while constantly stirring to get emulgel[7]

Evaluation Parameters:

The responders' rates (the primary efficacy parameter), defined as the percentage of participants who had an improvement in pain intensity as exhibited by a pain score reduction of at least one unit on the dental pain scale from baseline for two consecutive assessments any time between the five- and 20-minute points, were 87.3 percent, 80.7 percent and 70.4 percent, respectively, for 20 percent benzocaine gel, 10



percent benzocaine gel and vehicle gel. Both benzocaine gels were significantly ($P \leq .05$) better than vehicle gel; the 20 percent benzocaine gel also was significantly ($P \leq .05$) better than the 10 percent benzocaine gel. The mean amount of gel applied was 235.6 milligrams, with 88.2 percent of participants applying 400 mg or less. Under double-masked conditions, 576 participants self-applied study gel to an open tooth cavity and surrounding oral tissues. Participants evaluated their pain intensity and pain relief for 120 minutes. The authors determined the amount of gel the participants applied.[8]The study highlighted the effectiveness of frankincense-based moisturisers in the treatment of acne. It showed that frankincense helps in wound healing and reduces inflammation. The main aim of developing these formulations is to use frankincense for its dual role as both a cosmetic and a therapeutic ingredient, offering a natural and beneficial option for skin care.

As an alternative to synthetic treatments, the demand for natural skincare products is steadily increasing. Plant extracts that provide both cosmetic and therapeutic benefits are now widely used in topical formulations. Frankincense has become an important component of modern herbal skincare products due to its rich bioactive compounds and pleasant aroma. According to Rahman et al., frankincense plays a significant role in enhancing the effectiveness of herbal skincare formulations[9]. However, these studies also reported that some traditional medicines were either ineffective or toxic, and in some cases could lead to serious health complications. Therefore, there is a need for further research to confirm the effectiveness of herbal medicines and to develop safe, affordable, and efficient drugs for the treatment of common respiratory infections. This highlights the importance of analytical techniques, especially extraction methods, in studying the

bioactivity of medicinal plants. Such techniques play a crucial role in herbal medicine research and are closely linked to phytochemical, medicinal, and industrial applications. At present, there is no standardized extraction method for *Vitex negundo* Linn, as different studies continue to use various extraction techniques. Nevertheless, many studies have shown that these different methods are capable of producing a high yield of phytochemicals from *V. negundo* Linn. Therefore, this review focuses on exploring and comparing the different analytical methods and techniques used to extract common active secondary metabolites from *Vitex negundo* Linn[10]. *Withania somnifera* has been used for a very long time across all age groups, in both males and females, and even during pregnancy, without reported adverse effects. Traditionally, this plant has been valued for its antioxidant, adaptogenic, aphrodisiac, liver-protective, anti-inflammatory, and astringent properties. In recent years, it has also been used in the treatment of ulcers, bacterial infections, venom toxicity, and age-related cognitive decline. Clinical studies and animal experiments support the effectiveness of *Withania somnifera* in managing anxiety, cognitive and neurological disorders, inflammation, hyperlipidemia, and Parkinson's disease. Its chemopreventive properties suggest that it may serve as a beneficial supportive therapy for patients receiving radiation or chemotherapy. Additionally, recent research indicates that *Withania somnifera* may help reduce the development of tolerance and dependence associated with the long-term use of certain psychotropic drugs[11].

CONCLUSION

A combination of *Nirgundi*, *Boswellia*, and *Ashwagandha* in the form of a single topical gel is a synergistic and multi-location strategy to manage musculoskeletal pain and inflammation. Their



complementary action, i.e. the inhibition of prostaglandins to leukotrienes inhibition and cytokine regulation, allow good therapeutic potential. The contemporary formulation approaches also improve stability, bioavailability and acceptability of these herbal actives by the patients. Although this has been noted in the existing studies, the large scale clinical trials, characterization of extract standardization, and optimization of formulations are still required to prove long term safety, efficacy, and commercial feasibility. Generally, herbal pain relieving gels that feature these botanicals are an attractive alternative to standard analgesics in the natural world, that has good future chances of being pharmaceutically developed.

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