

Effectiveness and Safety of *Arnica montana* in Post-Surgical Setting, Pain and Inflammation

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Arnica montana has been widely used as a homeopathic remedy for the treatment of several inflammatory conditions in pain management and postoperative settings. This review gives an overview of the therapeutic use of *Arnica montana* in the above-mentioned fields also focusing on its mechanisms of action learned from animal models and *in vitro* studies. *Arnica montana* is more effective than placebo when used for the treatment of several conditions including post-traumatic and postoperative pain, edema, and ecchymosis. However, its dosages and preparations used have produced substantial differences in the clinical outcome. Cumulative evidence suggests that *Arnica montana* may represent a valid alternative to non-steroidal anti-inflammatory drugs, at least when treating some specific conditions.

Keywords: *Arnica montana*, homeopathy, herbal medicine, side effect profile, inflammation, pain, surgery, trauma, ecchymosis, edema

INTRODUCTION

The use of complementary therapies, including plant remedies, is widespread and rapidly expanding on a worldwide scale. Plant remedies are traditionally used in a variety of pharmacopoeias and on a large scale of doses, including extremely low-dose homeopathic formulations. Herbal medicine or botanical medicine or phytomedicine refers to the therapeutic use of herbs, herbal materials, herbal preparations, and finished herbal products containing plant

materials (seeds, berries, roots, leaves, bark, or flowers) or parts as active ingredients. Homeopathy is based on the concept “*similia similibus curentur*”¹ according to which symptoms, caused by the original substance in healthy subjects, can be reversed by the homeopathic remedy in patients having similar symptoms. Therefore, homeopathic drug administration is based on 3 principles: (1) the administration of an active element to healthy volunteers brings manifestation of a series of clinical symptoms at physical and psychological levels; (2) low doses of the same element(s) reverse pathological states in ill organisms presenting a similar symptomatologic pattern; (3) the homeopathic treatment retains its biological activity because of a peculiar method of dilution followed by vigorous shaking, that is, “*succussion*”, even if, after several successive serial dilutions, the probability of the presence of any active molecule is very low.^{2,3} There are several models attempting to explicate how the peculiar homeopathic procedure of succussion can change solvent structure at nanoscopic level and justify the permanence of pharmacological properties throughout dilutions.^{4–7}

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Arnica is one of the most popular medications in complementary medicine. This remedy can be extracted from several plant species belonging to the Asteraceae family including *Arnica montana*, *Arnica chamissonis*, *Arnica fulgens*, *Arnica cordifolia* and *Arnica sororia*, and it is widely sold as tincture, ointment, cream, gel, and tablet. In 2009, a study showed that Asteracea-containing remedies were frequently used in German primary care, and their uses were not associated with serious adverse reactions.⁸ *Arnica* can be used as a homeopathic or herbal remedy. There are also *Arnica*-based complex formulations which can include up to 32 different plant species which share morphological characteristics and therapeutic properties to treat inflammation, wounds, hematoma, and contusion.⁹ Among the different varieties, *Arnica montana* L. is one of the most used varieties and receives different local names including leopard's bane, wolf's bane, mountain tobacco, and mountain snuff.¹⁰ This herb (here referred as *Arnica*), native of the Siberian mountains and Central Europe, has been used for the treatment of numerous pathological conditions, including pain, stiffness, and swelling associated with trauma, contusions, sprains, myocarditis, cardiac insufficiency, arteriosclerosis, angina pectoris, postoperative clinical conditions, and for symptomatic relief in osteoarthritis.¹⁰⁻¹² In traditional medicine, patients suffering from traumatic disease often use *Arnica* as an "alternative" treatment, in the hope of resolving pain and reducing the use of conventional drugs which may cause adverse effects. Furthermore, according to a review concerning the use of alternative and complementary medicine for rheumatological conditions such as osteoarthritis, rheumatoid arthritis, and fibromyalgia, *Arnica* was used in 18% of patients attending the rheumatology department in a Mexican hospital.¹³ *In vitro* studies have shown that the most active components of *Arnica*, as well as of other members of the Asteraceae family, are helenalin and other sesquiterpene lactones such as 11 α ,13-dihydrohelenalin and chamissonolid. Early on, Lyss et al¹⁴ showed that helenalin inhibits the transcriptional factor nuclear factor kappa B (NF- κ B) through the alteration and stabilization of the NF- κ B/inhibitor of kappa B (IkappaB) complex in T cells, B cells, and epithelial cells and abrogates kappa B-driven gene expression. This represents one of the earliest evidences of the anti-inflammatory properties of *Arnica*. Later work showed that helenalin can inhibit human neutrophil migration and chemotaxis¹⁵ and activities of 5-lipoxygenase and leukotriene C4 synthase.¹⁶ Helenalin dose-dependently reduced cell-proliferation in cluster of differentiation (CD)⁴⁺ T cells after the activation of the mitochondrial apoptosis pathway and p53 rapid

stabilization and nuclear localization.¹⁷ Furthermore, it arrested activated CD4⁺ T cell cycle in the G2/M phase through an increase in p27^{KIP1}, p21^{WAF1/CIP1}, and cyclin D2, and a decrease in cyclin B1 and cyclin A.¹⁷ Helenalin also decreased the expression of cell-surface receptors CD25, CD28, CD27, and CD120b which play a key role in NF- κ B activation in T cells,¹⁷ supporting the mechanism proposed by Lyss et al in 1997.¹⁴ NF- κ B controls the transcription of various cytokine and adhesion molecule genes in addition to genes required for antigen presentation.¹⁸ NF- κ B activation is associated with the induction of pain and inflammation, as observed in animal models of inflammatory pain (rat carrageenan pleurisy and mouse carrageenan air pouch), characterized by the release of proinflammatory cytokines (tumor necrosis factor-alpha [TNF- α] and interleukin-1beta [IL-1 β]) and local recruitment of leukocytes.¹⁹ The ability of *Arnica* to inhibit activation of transcription factors NF- κ B and nuclear factor of activated T cells and proinflammatory cytokines IL-1 β and TNF- α correlate with their quantitative and qualitative content of sesquiterpene lactones.²⁰ Additionally, *Arnica* treatment showed a 4.5-fold inhibition of nitric oxide production, a reduction in the levels of inducible nitric oxide synthase and cyclooxygenase-2 protein, a 3-fold reduction in TNF- α level, and prevented nuclear translocation of NF- κ B in J774 murine macrophage cells challenged with lipopolysaccharide.²¹ Furthermore, in the rat, 21-day oral treatment with *Arnica* 30th centesimal dilution (30c) protected against hepatic mitochondrial membrane

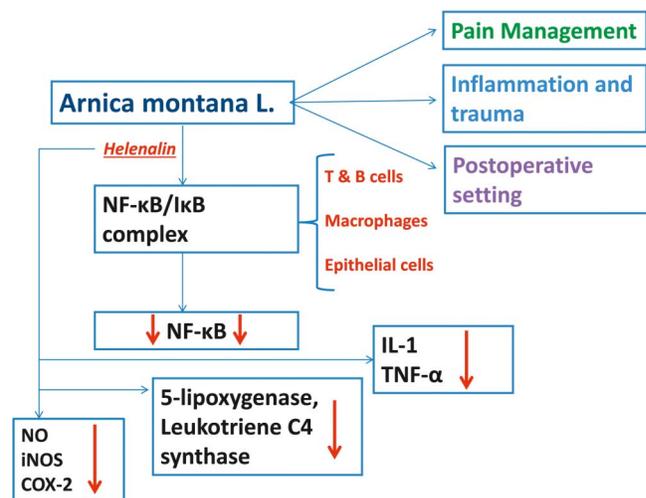


FIGURE 1. Mechanisms underlying *Arnica* effectiveness. COX-2, cyclooxygenase-2; TNF- α , tumor necrosis factor alpha; IL-1 β , interleukin-1 beta; NO, nitric oxide; iNOS, inducible nitric oxide synthase; NF- κ B, nuclear factor kappa B; I κ B, inhibitor of kappa B.

permeabilization induced by Ca^{2+} and/or Fe^{2+} -citrate-mediated lipid peroxidation and fragmentation of proteins due to attacks by reactive oxygen species.²² In Figure 1, we have summarized the mechanisms underlying *Arnica* effectiveness. As an herbal formulation, *Arnica* is generally used only topically (on the skin) because of side effects which can be observed after oral administration. Oral homeopathic remedies do contain *Arnica*, but they use an extremely diluted form which is not considered dangerous. The literature concerning *Arnica* in both phytotherapeutic and homeopathic formulations is rapidly increasing, together with the knowledge of its active principles and putative mechanisms of action. In this review, we grouped clinical evidence into 2 sections. The first group comprises the use of *Arnica* as topical formulation, either as a phytotherapeutic extract (higher dosage not succeeded) or homeopathic (diluted and succeeded preparations), whereas the second group comprises the use of homeopathic preparations administered by oral or topical route. The focus was on preclinical and clinical use of *Arnica* for the treatment of inflammatory conditions, in pain management and postoperative settings.

REVIEW CRITERIA

This review gives an overview of the literature in the aforementioned fields, from 1997 to 2013. The principal information sources are drawn from current reading of major complementary and alternative medicine journals, screening of the Hom-Inform Bibliographic Database and Information Service Databases (British Homeopathic Library, <http://hominform.soutron.com/>), literature search using MEDLINE, the Cochrane Database of Systematic Reviews, and cross-referencing among published articles. Our analysis includes controlled clinical trials (with and without randomization), observational studies, and case series, but it excludes single case reports. We also consulted previously published systematic reviews and meta-analyses which have covered the subject up to now. Finally, some relevant studies concerning the mechanism(s) of action and laboratory studies are reported.

PRECLINICAL STUDIES

Arnica has been used as a single remedy²³⁻²⁵ in preclinical models of acute (carrageenan- and homologous blood-induced rat paw edema) and chronic (nystatin-induced rat paw edema) inflammation and histamine-induced increased vascular permeability.²³⁻²⁶ For instance, autologous blood-induced edema was reduced 1, 3, and 5 hours after subplantar but not after oral administration

of *Arnica* 4th decimal dilution (4D), when compared with control animals.²³ Lussignoli et al²⁶ replicated this finding and showed that administration of *Arnica* alone or as a homeopathic formulation (Traumeel) an hour before or after the injection of autologous blood, decreased paw edema and enhanced the healing process. Reduction in paw edema coupled with a decrease in systemic interleukin-6 (IL-6) at 5 hours after blood edema induction.²⁶ Subchronic oral administration of *Arnica* 6c also reduced carrageenan-induced rat paw edema by 30%.²⁵ The reduction in paw edema was evident starting from 1 hour post-carrageenan, and lasted at least 6 hours. In the same study, oral treatment with *Arnica* 6c before 8.5% nystatin-induced inflammation showed a reduction in the edema at 6 hours compared with the control group. However, no effect was observed when administered after nystatin. Furthermore, *Arnica* 6c blocked histamine-induced increase in vascular permeability when administered 3 days before stimulus. Oral *Arnica* 6c administered every 15 minutes between 30 and 180 minutes, after 1% kappa carrageenan inoculation, was effective in reducing late but not early edema in the rat when compared with control groups.²⁴ Edema amelioration coupled with a decrease in the mast cell degranulation and an increase in the lymphatic vessel diameter. Helenalin, a sesquiterpene lactone and one of the main active constituent of *Arnica* extract,¹⁴ inhibited carrageenan-induced paw edema and complete Freund's adjuvant-induced arthritis in the rat.²⁷ Topical application of *Arnica* 3D gel (10%), combined with microcurrent (10 μA for 2 minutes) application, significantly improved wound healing in the linear incision wound model in the rat back.²⁸ The evidence was consistent with a significantly larger total number of cells and higher percentage of mature collagen fibers in the wound, as assessed by structural and morphometric analysis. Therefore, these results strongly support the relevance of *Arnica* in the treatment of inflammatory-related processes.

CLINICAL STUDIES

Topical applications of phytotherapeutic preparations

Up to now, several clinical trials involving the use of topical *Arnica* have been performed aiming to reduce laser-induced bruising and osteoarthritis-related symptoms. We have summarized these studies in Table 1.

Laser-induced bruising

Daily application of 2 extracts based on a combination of *Arnica* and stinging nettle (Combudoron liquid and Combudoron gel; 0.5 mL per lesion for 30 minutes for

Table 1. Clinical efficacy of *Arnica montana*.

Author(s), year	Design	No. Patients	Pathology	Treatment	Outcome	Herbal Homeopathy medicine
Kaziro, 1984 ²⁹	Randomized double-blind placebo-controlled trial	118	Post-surgical complications after removal of impacted wisdom teeth	<i>Arnica</i> 200c versus metronidazole versus placebo	Metronidazole was more effective in pain control ($P < 0.001$ and $P < 0.01$), swelling prevention ($P < 0.01$ and $P < 0.05$) and healing promotion ($P < 0.01$ and $P < 0.01$) when compared with <i>Arnica</i> and placebo, respectively	Yes
Albertini and Goldberg, 1986 ³⁰	Randomized placebo-controlled trial	30	Dental neuralgic pain after tooth extraction	<i>Arnica</i> 7c and <i>Hypericum</i> 15c versus placebo	76% of the patients treated with homeopathic remedies had pain relief versus 40% of patients receiving placebo	Yes
Zell et al, 1988 ³¹	Randomized double-blind placebo-controlled study	69	Acute sprains of the ankle joint	Traumeel ointment versus placebo	24 patients were pain-free on treatment day 10, whereas on the same day, only 13 patients treated with placebo had no pain	Yes
Dorfman et al, 1988 ³²	Double-blind, placebo-controlled clinical study	39	Prolonged venous perfusion	<i>Arnica</i> 5c	<i>Arnica</i> reduced pain, hyperemia, edema, and hematoma formation. Improvement in the blood flow and slight increase in coagulation factors and in platelet aggregation were observed after <i>Arnica</i> treatment	Yes
Baillargeon et al, 1993 ³³	Randomized double-blind, 2-period, crossover, clinical trial	18	Blood coagulation	<i>Arnica</i> 5c versus placebo	An increase in bleeding time and a decrease in fibrinogen were observed 30 minutes after <i>Arnica</i> administration	Yes
Lokken et al, 1995 ³⁴	Randomized double-blind, placebo-controlled crossover trial	24	Pain after surgical removal of bilaterally impacted mandibular third molars	<i>Arnica</i> 30D versus placebo	No difference in postsurgical pain was observed between <i>Arnica</i> and placebo. Postoperative swelling and bleeding were not significantly affected by homeopathy	Yes
Hart et al, 1997 ³⁵	Randomized double-blind controlled study	73	Pain and postoperative recovery after total abdominal hysterectomy	<i>Arnica</i> 30c versus placebo	No significant difference was observed between <i>Arnica</i> and placebo	Yes
Vickers et al, 1998 ³⁶	Randomized, double-blind placebo-controlled trial	400	Muscle soreness after long-distance running	<i>Arnica</i> 30D versus placebo	No significant change in muscle soreness after long-distance running was observed when comparing <i>Arnica</i> to placebo	Yes

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Table 1. (Continued) Clinical efficacy of *Arnica montana*.

Author(s), year	Design	No. Patients	Pathology	Treatment	Outcome	Herbal Homeopathy medicine
Ramelet et al, 2000 ³⁷	Randomized, prospective, multicenter double-blind trial	130	Saphenous stripping	<i>Arnica</i> 5c versus placebo	No significant difference in postoperative hematomas was observed between <i>Arnica</i> and placebo	Yes
Alonso et al, 2002 ¹¹	Randomized, double-blind placebo-controlled trial	19	Laser-induced bruising	<i>Arnica</i> gel versus vehicle	No difference was observed between <i>Arnica</i> and vehicle administered prior or after injury	Yes
Jeffrey and Belcher, 2002 ³⁸	Randomized double-blind, placebo-controlled study	37	Hand surgery (endoscopic carpal tunnel release)	<i>Arnica</i> 6D tablets and <i>Arnica</i> ointment versus placebo	No difference in grip strength or wrist circumference was found between <i>Arnica</i> and placebo. A significant reduction in pain was observed in the <i>Arnica</i> -treated group versus placebo. ($P = 0.03$)	Yes
Knuesel et al, 2002 ³⁹	Open multicenter trial	79	Mild–moderate knee osteoarthritis	<i>Arnica</i> gel	Median total scores on the Western Ontario and McMaster Osteoarthritis Index were significantly decreased in the intention-to-treat and per-protocol populations (both $P < 0.0001$). Scores on the pain, stiffness, and function subscales were also significantly decreased	Yes
Wolf et al, 2003 ³⁹	Prospective, randomized, double-blind, placebo-controlled pilot trial	60	Varicose vein surgery	<i>Arnica</i> 12D versus placebo	Hematoma surface was reduced with <i>Arnica</i> by 75.5% and with placebo by 71.5% (not significant). Pain score decreased by 1 ± 2.2 points with <i>Arnica</i> and 0.3 ± 0.8 points with placebo not significant The results of the study showed a trend towards a beneficial effect of <i>Arnica</i> regarding the reduction in hematoma and pain during the postoperative course	Yes
Stevinson et al, 2003 ³	Randomized double-blind placebo-controlled trial	62	Surgery for carpal tunnel syndrome	<i>Arnica</i> 6c or 30c versus placebo	No significant change in pain and bruising were observed after administration of <i>Arnica</i> or placebo	Yes

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Table 1. (Continued) Clinical efficacy of *Arnica montana*.

Author(s), year	Design	No. Patients	Pathology	Treatment	Outcome	Herbal Homeopathy medicine
Tveiten and Bruset, 2003 ⁴¹	Randomized double-blind placebo-controlled study	82	Muscle soreness and cell damage after marathon running	<i>Arnica</i> versus placebo	Muscle soreness immediately after the marathon was lower in the <i>Arnica</i> group versus placebo ($P = 0.04$)	Yes
Brinkhaus et al, 2006 ⁴²	Three randomized, placebo-controlled, double-blind, sequential clinical trials	227	Postoperative swelling and pain after arthroscopy, artificial knee joint implantation, and CLR	<i>Arnica</i> 30D versus placebo	<i>Arnica</i> was effective on swelling and pain only in the CLR trial ($P = 0.019$)	Yes
Seeley et al, 2006 ⁴³	Prospective randomized double-blind placebo-controlled study	29	Rhytidectomy	<i>Arnica</i> (SinEcch) versus placebo	Patients receiving <i>Arnica</i> had a smaller area of ecchymosis on postoperative days 1, 5, 7, and 10. These differences were statistically significant only on postoperative days 1 ($P < 0.005$) and 7 ($P < 0.001$)	Yes
Schneider et al, 2007 ⁴⁴	Multicenter, prospective, comparative observational cohort study	133	Musculoskeletal trauma and injuries	Traumeel versus conventional medicines	Complete resolution of pain and inflammatory symptoms at the end of therapy were observed in 59.4% of patients in the Traumeel group and in 57.8% of patients in the conventional medicine group	Yes
Robertson et al, 2007 ⁵²	Randomized double-blind, placebo-controlled trial	111	Tonsillectomy	<i>Arnica</i> 30c versus placebo	<i>Arnica</i> reduced pain scores ($P < 0.05$). No difference was observed in analgesia consumption, complications, and return to normal activities when comparing <i>Arnica</i> to placebo	Yes
Totonchi and Guyuron, 2007 ⁵¹	Randomized double-blind clinical study	48	Rhinoplasty	<i>Arnica</i> (SinEcch) versus intravenous dexamethasone plus oral tapering dose of methyl-prednisone or no treatment (control group)	<i>Arnica</i> and dexamethasone reduced swelling-edema if compared with control ($P < 0.0001$). <i>Arnica</i> and control group exhibited more resolution of ecchymosis if compared with dexamethasone ($P < 0.05$)	Yes
Widrig et al, 2007 ¹²	Randomized, double-blind study	204	Hand osteoarthritis	<i>Arnica</i> gel versus ibuprofen gel	<i>Arnica</i> and ibuprofen were equally effective for the treatment of hand osteoarthritis as	Yes

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Table 1. (Continued) Clinical efficacy of *Arnica montana*.

Author(s), year	Design	No. Patients	Pathology	Treatment	Outcome	Herbal Homeopathy medicine
Paris et al, 2008 ²	A phase 3 monocentric randomized placebo-controlled study	158	Knee ligament reconstruction	Granule composition containing <i>Arnica</i> 5c, <i>Bryonia alba</i> 5c, <i>Hypericum perforatum</i> 5c, and <i>Ruta graveolens</i> 3D versus placebo or no treatment	far as pain reduction, hand function, number of painful joints in both hands and intensity of morning stiffness in the worst affected hand were concerned Homeopathic treatment was not superior to placebo in reducing 24 h morphine consumption after knee ligament reconstruction. No significant difference in pain assessed by visual analog scale was observed between <i>Arnica</i> and placebo	Yes
Karow et al, 2008 ⁵³	Randomized double-blind, parallel-group study	88	Hallux valgus surgery	<i>Arnica</i> 4D versus diclofenac sodium	<i>Arnica</i> and diclofenac had equivalent efficacy on wound irritation, patient mobility, and use of analgesics. Diclofenac was more effective in reducing pain if compared with <i>Arnica</i> ($P = 0.027$)	Yes
Adkison et al, 2010 ⁴⁶	Randomized, double-blind, placebo-controlled trial	53	Leg pain after calf raises	<i>Arnica</i> cream versus placebo	<i>Arnica</i> increased pain scores if compared with placebo ($P < 0.005$). No difference in muscle tenderness and ankle motion was observed	Yes
Cornu et al, 2010 ⁴⁷	Double-blind placebo-controlled parallel trial	90	Aortic valve surgery	A combination of <i>Arnica montana</i> 5c and <i>Bryonia alba</i> 5c granules versus placebo	No difference between homeopathic treatment and placebo on bleeding, C-reactive protein, troponin I, and cumulated morphine was observed	Yes
Leu et al, 2010 ⁴⁸	Randomized, double-blind placebo-controlled trial	16	595-nm pulsed-dye laser-induced bruises on the bilateral upper inner arms	5% vitamin K versus 1% vitamin K and 0.3% retinol or 5% vitamin K or 20% <i>Arnica</i> or white petrolatum (placebo)	The mean improvement in bruising associated with 20% <i>Arnica</i> was greater than with white petrolatum ($P = 0.003$), and the mixture of 1% vitamin K and 0.3% retinol ($P = 0.01$) while improvement with <i>Arnica</i> was not greater than with 5% vitamin K cream	Yes
Huber et al, 2011 ⁴⁹	Single-blind, randomized trial	2	Erbium YAG-laser-induced grade-2 burns	Combudoron gel versus Combudoron liquid or placebo	Eschars treated with Combudoron fell off earlier if compared with placebo.	Yes

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Table 1. (Continued) Clinical efficacy of *Arnica montana*.

Author(s), year	Design	No. Patients	Pathology	Treatment	Outcome	Herbal Homeopathy medicine
Kucera et al, 2011 ⁵⁰	Randomized double-blind placebo- controlled study	570	Acute ankle joint distortion	gel or placebo liquid Combination of <i>Arnica</i> tincture and HES (spray) versus <i>Arnica</i> or HES or placebo	On day 3–4, improvement in pain on active motion was significantly higher in the <i>Arnica</i> + HES group if compared with the other 3 groups (t-test with unadjusted baseline values, $P < 4 \times 10^{-7}$ and ANCOVA after adjustment, $P < 5 \times 10^{-11}$)	Yes

CLR, cruciate ligament reconstruction; HES, hydroxyethyl salicylate.

7 days) was tested on erbium YAG laser-induced grade 2 burns. This single-blind randomized study involved 2 healthy male subjects receiving treatment or placebo on their backs at 4 sites. After 1 week of treatment, the diameters of the lesions were only slightly different between treatments. Most notably, the eschars treated with Combudoron fell off earlier than the placebo suggesting that Combudoron has a positive effect on burn healing.⁴⁹ In a randomized, double-blind 2-week study, twice a day topical application of *Arnica* 1× gel on one side of the face, before or after laser treatment was compared with vehicle application on the other hemiface in 19 patients affected by facial telangiectasias without improvement in visual analog scale (VAS) bruising.¹¹ Contrasting results were obtained in a 2-week double-blind randomized study including 16 healthy patients who underwent creation of 7-mm standard bruises on the upper inner arms by a 595-nm pulsed-dye laser.⁴⁸ Comparison of VAS-bruising scores indicated that 20% *Arnica* gel reduced bruising when compared with placebo and gel containing 1% vitamin K and 0.3% retinol, whereas comparison with 5% vitamin K gel did not show any significant difference.

Osteoarthritis

In a randomized, double-blind 3-week study which involved 204 patients affected by osteoarthritis of interphalangeal joints of the hands, topical application of a 4-cm gel strip of *Arnica* (50 g tincture/100 g) 3 times a day showed similar efficacy to ibuprofen (5%) gel in reducing pain, functional capacity of the hand, number of painful joints in both hands and intensity of morning stiffness in the worst affected hand.

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Orally administered homeopathic formulations

Homeopathic formulations of *Arnica* have been largely used in the clinical setting for the management of knee surgery, carpal tunnel syndrome, symptoms associated with wisdom teeth removal, rhytidectomy, rhinoplasty, abdominal hysterectomy, tonsillectomy, hallux valgus surgery, venous surgery, hemarthrosis, aortic valve surgery, prolonged venous perfusion, muscular pain, dental neuralgia, and ankle sprains.

Knee surgery

Brinkhaus et al⁴² tested the efficacy of oral administration of *Arnica* 30D administered as supplement to ordinary treatment (1 × 5 globules 2 hours before surgery plus 3 × 5 globules at 3-hour intervals post-operatively the day of surgery plus 3 × 5 globules until the last follow-up) on postoperative swelling and pain in patients undergoing different types of knee surgery in 3 consecutive randomized placebo-controlled clinical studies. *Arnica* reduced swelling and pain after cruciate ligament reconstruction (57 patients; last follow-up at day 8), but not after arthroscopy (227 patients; last follow-up at day 2), artificial knee joint implantation (35 patients; last follow-up at day 11), and cruciate ligament reconstruction (57 patients; last follow-up at day 8). Homeopathic treatment containing *Arnica* 5c, *Bryonia Alba* 5c, *Hypericum perforatum* 5c, and *Ruta graveolens* 3D (4-day treatment starting 1 day before the surgery; 5 granules per day) was not superior to placebo in reducing 24-hour morphine consumption after knee ligament reconstruction in a randomized controlled study including 158 patients.²

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Table 2. Studies on *Arnica montana* side effect profile.

Author(s), year	Formulation	Pathology	Side effect profile	Dose
Knuesel et al, 2002 ³⁹	Gel (topical application)	Knee osteoarthritis	One allergic reaction (not specified)	NS
Stevinson et al, 2003 ³	Tablets (oral treatment)	Hand surgery (carpal tunnel syndrome)	Dry mouth Headache Feeling "throbbly" in head/neck Drowsiness Sore tongue	<i>Arnica</i> 6c (for drowsiness and sore tongue) <i>Arnica</i> 30c (for dry mouth, headache, and feeling "throbbly")
Widrig et al, 2007 ¹²	Gel (topical application)	Hand osteoarthritis	Skin irritations Itching Reddening Allergic eczema Increased finger pain Bronchitis Chill Cystitis Rhinitis Vertigo	NS
Karow et al, 2008 ⁵³	Pills (oral treatment)	Hallux valgus surgery	Abdominal complaints Racing heart	<i>Arnica</i> 4D
Cornu et al, 2010 ⁴⁷	Granules (oral treatment)	Aortic valve surgery	Cardiovascular events (observed in both homeopathy and placebo groups)	<i>Arnica</i> 5c and <i>Bryonia alba</i> 5c
Kucera et al, 2011 ⁵⁰	Spray (topical application)	Ankle distortion	Burning, reddening, itching and urticaria were observed in the group receiving <i>Arnica</i> and hydroxyethyl salicylate. No adverse reactions were observed in patients receiving <i>Arnica</i> alone.	<i>Arnica</i> tincture: 41.5 mg Hydroxyethyl salicylate: 12.5 mg

NS, not specified in the article.

Carpal tunnel syndrome

In a double-blind randomized trial involving 62 patients, *Arnica* 30c or 6c administered daily from 7 days before to 14 days after surgery (3 tablets) was not effective in reducing bruising, swelling, and pain in patients undergoing elective surgery for carpal tunnel syndrome.³

Wisdom teeth removal

In a double-blind trial, *Arnica* 200c administered to 39 patients undergoing the removal of impacted wisdom

teeth, was less effective for pain and swelling management compared with placebo or metronidazole.²⁹ *Arnica* was also less effective in promoting healing when compared with metronidazole.²⁹ In a randomized double-blind placebo-controlled crossover trial including 24 patients undergoing prophylactic surgical removal of identical bilaterally impacted mandibular third molars, homeopathic treatment (30D) containing *Arnica*, *Hypericum*, *Staphysagria*, *Sedum*, *Phosphorus*, and *Plantago* did not produce any improvement in VAS pain score, postoperative bleeding and swelling and side effect profile when compared with the control

group.³⁴ Furthermore, a 33% less reduction in the ability to open the mouth was observed on day 3 after homeopathic treatment with *Arnica*. Ernst⁴⁵ criticized this study, arguing that the doses were fixed and the treatment schedule was not as flexible as homeopathy requires.

Rhytidectomy

Arnica (SinEcch, Alpine Pharmaceuticals, San Raphael, California; 1 dose every 8 hours for 4 days starting from the day of surgery) was used in patients undergoing rhytidectomy to evaluate its efficacy on bruising caused by facelift in a prospective randomized double-blind study including 29 patients.⁴³ A reduction in ecchymosis was observed at postoperative days 1 and 7 compared with placebo, as assessed by computer-measured skin color changes.

Rhinoplasty

In a randomized double-blind clinical study involving 48 primary rhinoplasty patients, oral *Arnica* (SinEcch) administered 3 times a day for 4 days and 10 mg intravenous dexamethasone administered intraoperatively and followed by a 6-day oral tapering dose of methyl-prednisone significantly reduced edema rating, but not intensity and extent of ecchymosis at day 2 post-rhinoplasty when compared with the control group. At postoperative day 8, *Arnica* and control group showed significantly less extent and intensity of ecchymosis when compared with dexamethasone group. Furthermore, no differences in edema rating were observed among groups at this time point.⁵¹

Abdominal hysterectomy

Negative results concerning the effect of *Arnica* 30c (2 doses preoperatively plus 3 doses postoperatively for 5 days) on pain, analgesia, infection, and postoperative recovery were obtained in a study including 73 women who underwent total abdominal hysterectomy.³⁵

Tonsillectomy

Arnica was tested in patients undergoing tonsillectomy. One hundred eleven patients undergoing tonsillectomy were randomized in a double-blind fashion to receive either *Arnica* 30c or placebo (2 tablets for 6 times in the first postoperative day followed by 2 tablets twice a day for 7 days).⁵² Follow-up over 14 days after surgery showed a significant reduction in the VAS pain scores, whereas no difference was observed

in analgesic consumption, complications and return to normal activities.

Hallux valgus surgery

Arnica 4D (pills; postoperatively 3 times a day for 4 days) was compared with diclofenac sodium 50 mg (postoperatively 3 times a day for 4 days) in a randomized double-blind clinical study in 88 patients undergoing hallux valgus surgery.⁵³ *Arnica* 4D and diclofenac sodium had equivalent efficacy on wound irritation, patient mobility, and use of analgesics, whereas *Arnica* was inferior to diclofenac sodium as far as VAS pain score was concerned.

Venous surgery

Arnica 5c, administered sublingually the night before and immediately after saphenous surgery, did not reduce postoperative hematomas, as evaluated 6 days postoperatively in a randomized, prospective, multicentric double-blind trial involving 130 patients.³⁷

Aortic valve surgery

Negative results were reported in a double-blind clinical study involving 90 patients undergoing aortic valve surgery assessing the efficacy of a combination of *Arnica* 5c and *Bryonia Alba* 5c.⁴⁷ Five homeopathic granules administered twice a day for 5 days, starting the evening before surgery for 5 days, did not produce any significant change in the volume of blood/liquid in the drains at their removal and postoperative blood/liquid losses at 12 and 24 hours as well as C-reactive protein, pain, temperature, and plasma troponin Ic.

Prolonged venous perfusion

In a double-blind, placebo-controlled clinical study involving patients undergoing prolonged venous perfusion, *Arnica* 5c reduced pain symptoms, hyperemia, edema, formation of hematomas and improved blood flow, as measured by Doppler flowmetry. *Arnica* treatment also slightly increased a number of coagulation factors and platelet aggregation.³²

Muscular pain

In a double-blind randomized study involving 82 marathon runners, 5 pills of *Arnica* 30D, given twice a day from the evening before until 3 days after the marathon, improved muscle soreness measured by VAS immediately after the competition, but it did not protect from cell damage (creatinine kinase, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, sodium, potassium, magnesium, and creatinine were analyzed) measured by

muscular enzymatic reaction.⁴¹ Contrasting results were reported in another double-blind randomized clinical study showing that *Arnica* 30D did not reduce muscle soreness after long-distance running in 519 runners, as assessed by VAS and Linkert scale.³⁶ In a randomized double-blind trial including 53 patients, *Arnica* cream applied immediately after performing calf raises and 24–48 hours post-exercise also failed to improve leg pain, motion, and muscle tenderness when compared with placebo.⁴⁶

Dental neuralgia

Arnica was effective for treatment of dental neuralgic pain after tooth extraction³⁰ in a placebo-controlled randomized clinical trial. *Arnica* 7c (4 granules) and *Hypericum* 15c (St John's wort; 4 granules) prescribed alternately at 4-hour intervals for 2 days, starting immediately after clinical examinations, resulted in pain relief experienced by 76% of patients treated with homeopathic combination therapy versus 40% of patients treated with placebo.

Ankle sprains

Arnica tincture spray (41.5 mg) was also tested in combination with hydroxyethyl salicylate (HES; 12.5 mg) and compared with *Arnica* (41.5 mg), HES (12.5 mg), and placebo for treatment of ankle joint distortion-related pain in a prospective, randomized, double-blind, 4-arm parallel group phase 4 study including 570 patients.⁵⁰ Application of *Arnica* plus HES 4–5 times daily improved pain assessed by VAS after quickly walking a distance of approximately 10 m on day 3–4. In summary, this study suggests that *Arnica* can act synergistically with other medications such as HES to reduce sprained ankle joint distortion-related pain.

SAFETY OF ARNICA FORMULATIONS

Although the use of homeopathic medicines is growing, these compounds are often deemed safe and risk-free with patients not declaring their use to their general practitioner. Little evidence is available concerning the use of *Arnica* in pediatric patients. In this regard, herbal products are extensively used to treat children without consulting the pediatrician and without reporting their use before a surgical procedure, as showed in a study by Crowe and Lyons.⁵⁴ In this study, the parents of 601 children undergoing ambulatory surgery were asked to fill in a questionnaire about the administration of herbal medicines to their children. Sixty-six percent of children were taking herbal medicines (*Arnica* and *Echinacea* were most commonly used) or had taken them in the past, and

84.7% of parents had not told the practitioner about their use, without thinking that herbal products could lead to adverse effects and interact with anesthetic drugs and the surgical procedure itself. These observations confirm that homeopathic drugs may be used safely either in general practice or on self-prescription, although the general practitioner should be informed to avoid a delay in the choice of a classic drug treatment, if required. Further evidence shows that *Arnica* can be used for external and internal bruising of both mother and newborn infant.⁵⁵ Furthermore, *Arnica* has been extensively used for soft-tissue bruising in a cohort of patients from birth to 8.5 years of age [Avon Longitudinal Study of Parents and Children (ALSPAC)].⁵⁶ A further study involving 6323 babies showed efficacy and safety of *Arnica Echinacea* powder in the detachment of the umbilical cord (detachment times: 2 days in 5.12%, 3 days in 44.23%, 4 days in 39.74%, 5 days in 3.20%, 6 days in 3.84%, 7 and 8 days in 1.92%, and 9 days in 0.64%) recommending its use as routine procedure in all nurseries.⁵⁷

As far as safety and adverse events in the adult population are concerned, *Arnica* administered topically is generally well tolerated, particularly as gel formulation.^{12,39} Only 1 allergic reaction was reported by Knuesel et al³⁹ after topical application of *Arnica* for the treatment of mild-to-moderate knee osteoarthritis. Widrig et al¹² reported side effects occurring only in 5 out of 89 patients receiving *Arnica* gel for the treatment of hand osteoarthritis. A further clinical trial of topical *Arnica* gel treatment for laser-induced bruises did not report any adverse reactions.¹¹ Another report evaluated the irritating and sensitizing potential of *Arnica* on 22 subjects without observing any adverse effects.⁵⁸ When administered orally, *Arnica* is safe and well tolerated only at very low concentrations, such as those used in homeopathic medicines.^{40,59} Therefore, *Arnica's* good tolerability and efficacy proved that *Arnica* in gel formulation, as well as in homeopathic dilutions for oral use, is an important therapeutic agent which can be used for pain relief, post-traumatic edema, and in the postoperative setting. Furthermore, in certain cases, such as local and generalized pain, the simultaneous administration of topical and orally administered *Arnica*, besides being safe and well tolerated, is indicated³⁸ because of the therapeutic synergy created between the two administration routes. We have summarized the studies reporting on *Arnica* side effect profile in Table 2.

DISCUSSION

Over the past twenty years, the use of homeopathic medicines has increased worldwide in terms of both

prescriptions by physicians and increased recommendation by pharmacists. In particular, *Arnica* is one of the homeopathic remedies used for over 100 years for the treatment of trauma-associated pain and swelling. This review summarizes the available preclinical and clinical evidence concerning the efficacy and safety of the homeopathic product *Arnica* in pain-related processes. Overall, *Arnica* (topical and/or oral formulations) has demonstrated reproducible clinical benefits, some of which are comparable with anti-inflammatory drugs such as diclofenac,⁵³ ibuprofen^{12,60} and corticosteroids⁵¹ which are considered the therapeutics of choice for the treatment of osteoarthritis, postoperative edema, and ecchymosis.⁶¹

Although limited evidence is available for the use of *Arnica* in the context of wound healing, a study suggests that it can be used instead of diclofenac after hallux valgus surgery to reduce wound irritation and at a lower cost.⁵³ Furthermore, combined with stinging nettle, it showed promising results in 2 patients with grade 2 laser-induced burns.⁴⁹ In patients undergoing the removal of impacted wisdom teeth, *Arnica* was less effective for the management of pain and swelling compared with placebo suggesting that it should not be used in that clinical condition.²⁹ These findings suggest that *Arnica* can be used in the context of wound healing in selected clinical scenarios. However, the limited number of studies warrants further investigations. The topical use of *Arnica* is supported by studies evincing its efficacy in relieving acute muscle pain after excessive exercise,⁶² and in the symptomatic treatment of osteoarthritis.^{12,39} The local action is exerted: (1) at the level of the locomotor system on the muscles, calming the feeling of soreness and pain⁶³; (2) in the joints, reducing the swelling and pain caused by rheumatic disorders; (3) in the capillaries and veins, reducing hematoma and ecchymosis and protecting blood vessels.^{20,62} Additionally, *Arnica* administered orally in homeopathic dilutions showed positive clinical effects in reducing postoperative pain, swelling, edema, and ecchymosis.^{40,42,51,52} Furthermore, topical *Arnica* combined with oral homeopathic dilutions significantly reduced postoperative pain.³⁸ As to topical gels, this review points out that *Arnica* has clinical benefits in relieving pain and surgical complications. The topical application of *Arnica* thus offers an alternative to ibuprofen because of the high concentration of sesquiterpenes,¹² and in particular helenalin, which is the active substance held responsible for its anti-inflammatory activity.¹⁴ The level of sesquiterpenes depends on multiple factors. For example, Douglas et al⁶⁴ showed that the total amount of bioactive endogenous sesquiterpenes varies depending on which portion of the plant is being used. The

concentration of sesquiterpenes was found to be higher in the disc florets than in the ray florets, lower in the receptacle, and even lower in the stalk.⁶⁴ This variability in the quantity of sesquiterpenes, with a consequent variation in the biological activity, can influence the clinical efficacy of *Arnica*.²⁰ To guarantee the efficacy of medicines containing *Arnica*, it is necessary to obtain a phytocomplex with optimal levels of active substances. This requires the use of high-quality raw material that is obtained by harvesting whole, fresh and spontaneously occurring *Arnica* in its natural habitat, far from any form of pollution and during the balsamic phase. Reproducibility is assured by accurate botanical identification, safeguarding the freshness of the batch, and performing checks on the raw material and the finished product. The quality and safety of homeopathic medicines containing *Arnica* are guaranteed by the European Pharmacopoeia and by specific *Arnica* monographs included in the pharmacopoeias of the individual member states. Pharmaceutical companies which produce homeopathic medicines containing *Arnica* in compliance with these standards are able to guarantee its efficacy and safety. Specifically, *Arnica* use in various clinical settings is achieving a wider reputation supported by an arising number of open studies, even if comparison of this compound with traditional drugs has been rarely performed.

CONCLUSIONS

Cumulative evidence suggests that both *Arnica* in gel formulation and in homeopathic dilutions are more effective than placebo in treating several inflammatory conditions, in pain management and postoperative settings. Its clinical efficacy in these fields and its high tolerability make it a potential therapeutic alternative target to non-steroidal anti-inflammatory drugs, especially for patients undergoing pharmacological polytherapy as they are more exposed to the risk of drug interactions and, consequently, to their toxicity. The wide variability of formulations and therapeutic settings precludes a meta-analysis that could assess the efficacy of specific protocols. Further trials involving larger cohorts of patients are needed to support a possible effect of *Arnica* in several inflammatory conditions, in pain management and postoperative settings.

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