

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

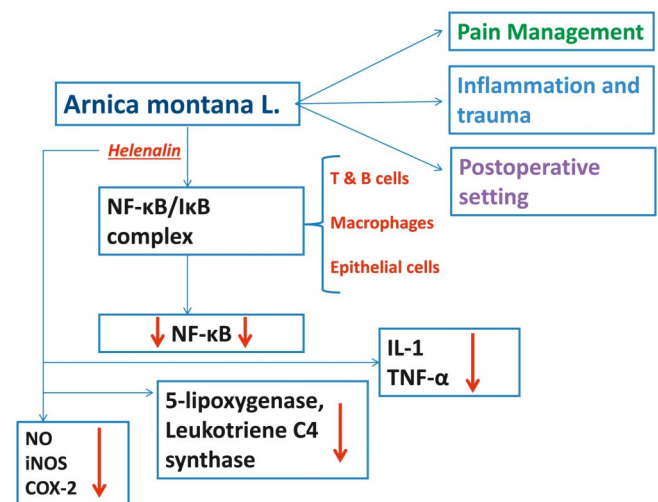


FIGURE 1. Mechanisms underlying *Arnica* effectiveness. COX-2, cyclooxygenase-2; TNF- α , tumor necrosis factor alpha; IL-1 β , interleukin-1 beta; NO, nitric oxide; iNOS, inducible nitric oxide synthase; NF- κ B, nuclear factor kappa B; I κ B, inhibitor of kappa B.

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 succussed) or homeopathic (diluted and succussed 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 remedy^{23–25} 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

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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

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Table 1. Clinical efficacy of *Arnica montana*.

| Author(s), year | Design | No. Patients | Pathology | Treatment | Outcome | Homeopathy | Herbal 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 | Yes | |

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

| Author(s), year | Design | No. Patients | Pathology | Treatment | Outcome | Homeopathy | Herbal medicine |
|---|---|--------------|---|--|--|------------|-----------------|
| 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 | after <i>Arnica</i> administration 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 | |
| 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 | | Yes |

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

| Author(s), year | Design | No. Patients | Pathology | Treatment | Outcome | Homeopathy | Herbal medicine |
|------------------------------------|---|--------------|------------------------------------|--|--|------------|-----------------|
| Knuesel et al, 2002 ³⁹ | Open multicenter trial | 79 | Mild–moderate knee osteoarthritis | <i>Arnica</i> gel | placebo. A significant reduction in pain was observed in the <i>Arnica</i> -treated group versus placebo. ($P = 0.03$) 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 | |
| | | 82 | | <i>Arnica</i> versus placebo | Muscle soreness immediately after the | Yes | |

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

| Author(s), year | Design | No. Patients | Pathology | Treatment | Outcome | Homeopathy | Herbal medicine |
|---|--|--------------|--|--|--|------------|-----------------|
| Tveiten and Brusset, 2003 ⁴¹ | Randomized double-blind placebo-controlled study | | Muscle soreness and cell damage after marathon running | | marathon was lower in the <i>Arnica</i> group versus placebo ($P = 0.04$) | | |
| 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 | Yes | |

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

| Author(s), year | Design | No. Patients | Pathology | Treatment | Outcome | Homeopathy | Herbal medicine |
|--|---|--------------|------------------------------|---|---|------------|-----------------|
| 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) | comparing <i>Arnica</i> to placebo <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 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 | Yes | |
| 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 | 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 | Yes | |

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

| Author(s), year | Design | No. Patients | Pathology | Treatment | Outcome | Homeopathy | Herbal medicine |
|-----------------------------------|--|--------------|---|--|--|------------|-----------------|
| Adkison et al, 2010 ⁴⁶ | Randomized, double-blind, placebo-controlled trial | 53 | Leg pain after calf raises | <i>Arnica</i> cream versus placebo | mobility, and use of analgesics. Diclofenac was more effective in reducing pain if compared with <i>Arnica</i> ($P = 0.027$) <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 gel or placebo liquid | 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 | Homeopathy | Herbal medicine |
|----------------------------------|--|--------------|------------------------------|--|---|------------|-----------------|
| Kucera et al, 2011 ⁵⁰ | Randomized double-blind placebo-controlled study | 570 | Acute ankle joint distortion | 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.

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.

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 postoperatively 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

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 I.

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 (creatine 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.

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.

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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REFERENCES

1. WHO. *Safety Issues in the Preparation of Homeopathic Medicines*. Geneva, Switzerland: World Health Organization documents; 2009. Available at: <http://www.who.int/medicines/areas/traditional/Homeopathy.pdf?ua=1>.
2. Paris A, Gonnet N, Chaussard C, et al. Effect of homeopathy on analgesic intake following knee ligament reconstruction: a phase III monocentre randomized placebo controlled study. *Br J Clin Pharmacol*. 2008;65:180–187.
3. Stevinson C, Devaraj VS, Fountain-Barber A, et al. Homeopathic arnica for prevention of pain and bruising: randomized placebo-controlled trial in hand surgery. *J R Soc Med*. 2003;96:60–65.
4. Bellavite P, Marzotto M, Oliosio D, et al. High-dilution effects revisited. 1. Physicochemical aspects. *Homeopathy*. 2014;103:4–21.
5. Bellavite P, Marzotto M, Oliosio D, et al. High-dilution effects revisited. 2. Pharmacodynamic mechanisms. *Homeopathy*. 2014;103:22–43.
6. Bell IR, Koithan M. A model for homeopathic remedy effects: low dose nanoparticles, allostatic cross-adaptation, and time-dependent sensitization in a complex adaptive system. *BMC Complement Altern Med*. 2012;12:191.
7. Roy R, Tiller W, Bell IR, et al. The structure of liquid water. Novel insights from materials research; potential relevance to homeopathy. *Mat Res Innovat*. 2005;9:98–103.
8. Jeschke E, Ostermann T, Luke C, et al. Remedies containing Asteraceae extracts: a prospective observational study of prescribing patterns and adverse drug reactions in German primary care. *Drug Saf*. 2009;32:691–706.
9. Obon C, Rivera D, Verde A, et al. Arnica: a multivariate analysis of the botany and ethnopharmacology of a medicinal plant complex in the Iberian Peninsula and the Balearic Islands. *J Ethnopharmacol*. 2012;144:44–56.
10. Lawrence WT. Arnica. *Plast Reconstr Surg*. 2003;112:1164–1166.
11. Alonso D, Lazarus MC, Baumann L. Effects of topical arnica gel on post-laser treatment bruises. *Dermatol Surg*. 2002;28:686–688.
12. Widrig R, Suter A, Saller R, et al. Choosing between NSAID and arnica for topical treatment of hand osteoarthritis in a randomised, double-blind study. *Rheumatol Int*. 2007;27:585–591.
13. Alvarez-Hernandez E, Cesar Casasola-Vargas J, Lino-Perez L, et al. Complementary and alternative medicine in patients attending a rheumatology department for the first time. Analysis of 800 patients. *Reumatol Clin*. 2006;2:183–189.
14. Lyss G, Schmidt TJ, Merfort I, et al. Helenalin, an anti-inflammatory sesquiterpene lactone from Arnica, selectively inhibits transcription factor NF-kappaB. *Biol Chem*. 1997;378:951–961.
15. Hall IH, Starnes CO Jr, Lee KH, et al. Mode of action of sesquiterpene lactones as anti-inflammatory agents. *J Pharm Sci*. 1980;69:537–543.
16. Tornhamre S, Schmidt TJ, Nasman-Glaser B, et al. Inhibitory effects of helenalin and related compounds on 5-lipoxygenase and leukotriene C(4) synthase in human blood cells. *Biochem Pharmacol*. 2001;62:903–911.
17. Berges C, Fuchs D, Opelz G, et al. Helenalin suppresses essential immune functions of activated CD4+ T cells by multiple mechanisms. *Mol Immunol*. 2009;46:2892–2901.
18. Baeuerle PA, Henkel T. Function and activation of NF-kappa B in the immune system. *Annu Rev Immunol*. 1994;12:141–179.

19. Lawrence T, Gilroy DW, Colville-Nash PR, et al. Possible new role for NF-kappaB in the resolution of inflammation. *Nat Med*. 2001;7:1291–1297.
20. Klaas CA, Wagner G, Laufer S, et al. Studies on the anti-inflammatory activity of phytopharmaceuticals prepared from Arnica flowers. *Planta Med*. 2002;68:385–391.
21. Verma N, Tripathi SK, Sahu D, et al. Evaluation of inhibitory activities of plant extracts on production of LPS-stimulated pro-inflammatory mediators in J774 murine macrophages. *Mol Cell Biochem*. 2010;336:127–135.
22. de Camargo RA, da Costa ED, Catisti R. Effect of the oral administration homeopathic Arnica montana on mitochondrial oxidative stress. *Homeopathy*. 2013;102:49–53.
23. Conforti A, Bellavite P, Bertani S, et al. Rat models of acute inflammation: a randomized controlled study on the effects of homeopathic remedies. *BMC Complement Altern Med*. 2007;7:1.
24. Kawakami AP, Sato C, Cardoso TN, et al. Inflammatory process modulation by homeopathic arnica montana 6CH: the role of individual variation. *Evid Based Complement Alternat Med*. 2011;2011:917541.
25. Macedo SB, Ferreira LR, Perazzo FF, et al. Anti-inflammatory activity of Arnica montana 6CH: preclinical study in animals. *Homeopathy*. 2004;93:84–87.
26. Lussignoli S, Bertani S, Metelmann H, et al. Effect of Traumeel S, a homeopathic formulation, on blood-induced inflammation in rats. *Complement Ther Med*. 1999;7:225–230.
27. Hall IH, Lee KH, Starnes CO, et al. Anti-inflammatory activity of sesquiterpene lactones and related compounds. *J Pharm Sci*. 1979;68:537–542.
28. Castro FC, Magre A, Cherpinski R, et al. Effects of micro-current application alone or in combination with topical Hypericum perforatum L. and Arnica montana L. on surgically induced wound healing in Wistar rats. *Homeopathy*. 2012;101:147–153.
29. Kaziro GS. Metronidazole (Flagyl) and Arnica montana in the prevention of post-surgical complications, a comparative placebo controlled clinical trial. *Br J Oral Maxillofac Surg*. 1984;22:42–49.
30. Albertini H, Goldberg W. *Évaluation d'un traitement homéopathique de le névralgie dentaire. Bilan de 60 observations dentaires en recherches en homéopathie*. Lyon, France: Fondat. Franc. Rech. Homéopath; 1986:75.
31. Zell J, Connert WD, Mau J, et al. Treatment of acute sprains of the ankle joint. Double-blind study assessing the effectiveness of a homeopathic ointment preparation. *Fortschr Med*. 1988;106:96–100.
32. Dorfman P, Amodeo C, Ricciotti F, et al. Évaluation de l'activité de l'Arnica 5CH sur les troubles veineux après perfusion prolongée. *Cahiers de Biothérapie* 1988;98 (Suppl):77–82.
33. Baillargeon L, Drouin J, Desjardins L, et al. The effects of Arnica montana on blood coagulation. Randomized controlled trial. *Can Fam Physician*. 1993;39:2362–2367.
34. Lokken P, Straumsheim PA, Tveiten D, et al. Effect of homeopathy on pain and other events after acute trauma: placebo controlled trial with bilateral oral surgery. *BMJ*. 1995;310:1439–1442.
35. Hart O, Mullee MA, Lewith G, et al. Double-blind, placebo-controlled, randomized clinical trial of homeopathic arnica C30 for pain and infection after total abdominal hysterectomy. *J R Soc Med*. 1997;90:73–78.
36. Vickers AJ, Fisher P, Smith C, et al. Homeopathic Arnica 30x is ineffective for muscle soreness after long-distance running: a randomized, double-blind, placebo-controlled trial. *Clin J Pain*. 1998;14:227–231.
37. Ramelet AA, Buchheim G, Lorenz P, et al. Homeopathic Arnica in postoperative haematomas: a double-blind study. *Dermatology*. 2000;201:347–348.
38. Jeffrey SL, Belcher HJ. Use of Arnica to relieve pain after carpal-tunnel release surgery. *Altern Ther Health Med*. 2002;8:66–68.
39. Knuesel O, Weber M, Suter A. Arnica montana gel in osteoarthritis of the knee: an open, multicenter clinical trial. *Adv Ther*. 2002;19:209–218.
40. Wolf M, Tamaschke C, Mayer W, et al. Efficacy of Arnica in varicose vein surgery: results of a randomized, double-blind, placebo-controlled pilot study. *Forsch Komplementarmed klass Naturheilkd*. 2003;10:242–247.
41. Tveiten D, Bruslet S. Effect of Arnica D30 in marathon runners. Pooled results from two double-blind placebo controlled studies. *Homeopathy*. 2003;92:187–189.
42. Brinkhaus B, Wilkens JM, Ludtke R, et al. Homeopathic arnica therapy in patients receiving knee surgery: results of three randomised double-blind trials. *Complement Ther Med*. 2006;14:237–246.
43. Seeley BM, Denton AB, Ahn MS, et al. Effect of homeopathic Arnica montana on bruising in face-lifts: results of a randomized, double-blind, placebo-controlled clinical trial. *Arch Facial Plast Surg*. 2006;8:54–59.
44. Schneider C, Schnieder B, Hanisch J, et al. The role of a homeopathic preparation compared with conventional therapy in the treatment of injuries: an observational cohort study. *Complement Ther Med*. 2008;16:22–27.
45. Ernst E. Effects of homeopathy. Trial did not evaluate "true" homeopathy. *BMJ*. 1995;311:510–511.
46. Adkison JD, Bauer DW, Chang T. The effect of topical arnica on muscle pain. *Ann Pharmacother*. 2010;44:1579–1584.
47. Cornu C, Joseph P, Gaillard S, et al. No effect of a homeopathic combination of Arnica montana and Bryonia alba on bleeding, inflammation, and ischaemia after aortic valve surgery. *Br J Clin Pharmacol*. 2010;69:136–142.
48. Leu S, Havey J, White LE, et al. Accelerated resolution of laser-induced bruising with topical 20% arnica: a rater-blinded randomized controlled trial. *Br J Dermatol*. 2010;163:557–563.
49. Huber R, Bross F, Schempp C, et al. Arnica and stinging nettle for treating burns - a self-experiment. *Complement Ther Med*. 2011;19:276–280.
50. Kucera M, Kolar P, Barna M, et al. Arnica/Hydroxyethyl salicylate combination spray for ankle distortion: a four-arm randomised double-blind study. *Pain Res Treat*. 2011;2011:365625.

51. Totonchi A, Guyuron B. A randomized, controlled comparison between arnica and steroids in the management of postrhinoplasty ecchymosis and edema. *Plast Reconstr Surg*. 2007;120:271–274.
52. Robertson A, Suryanarayanan R, Banerjee A. Homeopathic *Arnica montana* for post-tonsillectomy analgesia: a randomised placebo control trial. *Homeopathy*. 2007;96:17–21.
53. Karow JH, Abt HP, Frohling M, et al. Efficacy of *Arnica montana* D4 for healing of wounds after Hallux valgus surgery compared to diclofenac. *J Altern Complement Med*. 2008;14:17–25.
54. Crowe S, Lyons B. Herbal medicine use by children presenting for ambulatory anesthesia and surgery. *Paediatr Anaesth*. 2004;14:916–919.
55. Kaplan B. Homeopathy: 2. In pregnancy and for the under-fives. *Prof Care Mother Child*. 1994;4:185–187.
56. Thompson EA, Bishop JL, Northstone K. The use of homeopathic products in childhood: data generated over 8.5 years from the Avon Longitudinal Study of Parents and Children (ALSPAC). *J Altern Complement Med*. 2010;16:69–79.
57. Perrone S, Coppi S, Coviello C, et al. Efficacy of *Arnica Echinacea* powder in umbilical cord care in a large cohort study. *J Matern Fetal Neonatal Med*. 2012;25:1111–1113.
58. Final report on the safety assessment of *Arnica montana* extract and *Arnica montana*. *Int J Toxicol*. 2001;20(Suppl 2):1–11.
59. DerMarderosian A, Beutler JA, eds. *Facts and Comparisons: The Review of Natural Products*. St. Louis, MO: Wolters Kluwer; 2001.
60. Ross SM. Osteoarthritis: a proprietary *Arnica* gel is found to be as effective as ibuprofen gel in osteoarthritis of the hands. *Holist Nurs Pract*. 2008;22:237–239.
61. Moore RA, Tramer MR, Carroll D, et al. Quantitative systematic review of topically applied non-steroidal anti-inflammatory drugs. *BMJ*. 1998;316:333–338.
62. Schmidt C. A double-blind, placebo-controlled trial: *arnica montana* applied topically to Subcutaneous mechanical Injuries. *J Am Inst Homeopathy*. 1996;89:186.
63. Merfort I. *Arnica*: new insights on the molecular mode of action of a traditional medicinal plant. *Forsch Komplementarmed klass Naturheilkd*. 2003;10(Suppl 1):45–48.
64. Douglas JA, Smallfield BM, Burgess EJ, et al. Sesquiterpene lactones in *Arnica montana*: a rapid analytical method and the effects of flower maturity and simulated mechanical harvesting on quality and yield. *Planta Med*. 2004;70:166–170.