Chapter 4
Arnica montana L.: Traditional Uses, Bioactive Chemical Constituents, and Pharmacological Activities

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Abstract *Arnica montana*, is a hemicryptophyte plant, belongs to the Asteraceae family. It is a medicinally significant herb that is used in traditional medicine systems in many countries. Flowers, roots, and rhizomes of *Arnica* are traditionally used for the topical treatments of various ailments such as bruises, sprains, backache, rheumatic arthritis, and phlebitis. Sesquiterpene lactones, flavonoids, fatty acids, thymol derivatives, and chlorogenic acid are the main bioactive phytochemicals. Extract and compounds from *A. montana* exhibited several pharmacological activities: anti-inflammatory, anticancer, antioxidant, antimicrobial, antiplatelets, and immunomodulatory activities. Helenalin and dihydrohelinalin are mainly responsible for their anti-inflammatory properties. The clinical trial using gel, cream, oil, ointment, and homeopathic dilutions revealed significant effects in relieving postoperative pains, surgical complications, swelling, edema, and ecchymosis. Different clinical trials using randomized placebo-controlled, randomized double-blinded, and open multicenter trials against different diseases reflect the medicinal importance of this plant. The aim of this chapter is to insight knowledge about the traditional uses, chemical compositions, pharmacological activities, and clinical trials of the plant *Arnica montana*. In vitro in in vitro.

Keywords *Arnica montana* · Homeopathy · Sesquiterpene lactones · Anti-inflammatory · Placebo-controlled

4.1 Introduction

The species *Arnica montana*, mostly distributed in Europe, belongs to the Asteraceae family. It comprises two subspecies: one is *Arnica montana* ssp. *montana* distributed in Central Europe and Scandinavia, and the other is *Arnica montana* ssp. *atlantica* distributed in southern France Portugal and Spain. It is commonly

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H. P. Devkota, T. Aftab (eds.), *Medicinal Plants of the Asteraceae Family*,
https://doi.org/10.1007/978-981-19-6080-2_4

recognized as leopard's bane, wolf's bane, and mountain tobacco by local people. Most frequently it is also identified as mountain snuff, mountain arnica, and sneezing tree. It is a flowering perennial plant that extent up to 30–60 cm tall. It has an aromatic fragrance. *Arnica* is derived from the Latin word "Ptarnica," which means "sneeze-making" (Maryna et al. 2019). It blooms in July and August with beautiful yellow daisy-like flowers. The length of beam flowers teeth is no longer than 1 mm or lies between 1 and 2 mm. Similarly, the dimension of the second flower differs from 4.9 to 5.7 cm (Kriplani et al. 2017). It grows in damp, grassy highland meadows in Europe, Northern Asia, and Siberia's mountains and hills. It is a reliable bioindicator for nutrient-deficient soils (Hollmann et al. 2020). The active constituents of this plant are mainly flavonoids (quercetin along with its derivatives like quercetin-3-glyco galacturonic and quercetin-3-mono-glucosideo) (Ganzera et al. 2008), sesquiterpene lactones (arnicolide, 11α, 13-dihydro-helenaline and helenaline) (Jürgens et al. 2022), alcohols (arnidiol, isoarnilenediol, arnilenediol), tannins, essential oil, carotenoids, inulin, and fatty acids (Macêdo et al. 2004). Among these, the main active compounds in *A. montana* flower heads are sesquiterpene lactones of the pseudo guaianolide group that is capable of the development of anti-inflammatory drugs (Kriplani et al. 2017). *Arnica* has been utilized in the homeopathic medicine of treatment for millennia. It is used to treat 66 different pathological conditions; however, most favorably treats contusions, wounds, rheumatism, and inflammation (Kriplani et al. 2017). Regrettably, several European countries have considered this species in endangered list including Bosnia and Herzegovina, Sweden, Spain, Hungary, Croatia, Slovenia, Germany, Lithuania, and Luxembourg. Most of the Europen countries has increased cultivation for its protection, but harvesting is prohibited in Italy (Aiello et al. 2012; Kawakami et al. 2011; Stanik et al. 2020). *A. montana* thrives at elevations of 500–2500 m, less fertile grasslands and peat bogs, as well as in soils with lower pH value. It is herbaceous plant with bushy stems, dark green basal, and lower cauline leaves (Kriplani et al. 2017; Aiello et al. 2012). A fruit is seed like cylindrical shaped having shiny whitish color and a plumose pap-pus (Kriplani et al. 2017).

Arnica montana is a medicinally significant herb which is exploited in homeopathy and pharmacy. For medicinal uses, various plant components such as rhizomes, roots, inflorescences, and leaves are harvested. Terpenoids, sesquiterpenes, sesquiterpene lactones, essential oils, phenolic acids, and flavonoids, particularly chlorogenic acids, are all abundant in *Arnica* (Ganzera et al. 2008). Various factors such as habitat, temperature, altitude, different climate conditions, and maturity period affect the chemical composition of this plant (Spitaler et al. 2008). The origin and versatility of ethno-pharmacological categories on medicinal herb *Arnica* offers an interesting field of drug discovery (Obón et al. 2012). *Arnica* leaves, flowers, and roots have been used for therapeutic cures in human beings and veterinarian phytotherapy. Raw materials of this plant are generally used in cosmetics, certain European liquors, and natural flavoring agents (Kouzi and Nuzum 2007). *Arnica*'s tolerance and efficacy also demonstrated that it is a significant treatment modality for relief in pain, posttraumatic edema, and postoperative context, both in formulating gel and homeopathic dilutions for oral administration (Iannitti et al. 2016).

The purpose of this chapter is to sum up evidence of using *Arnica* as an alternative approach for traditional use, chemical composition, ethnopharmacology, and therapeutic drugs that promote future research and development on this valuable medicinal herb. It will provide brief descriptions from clinical trials testing of *Arnica* on relief in pain, surgery, implant placements, and seroma reduction along with a discussion of possible mechanisms of action, safety, toxicity, and it's adverse effects.

4.2 Traditional Uses

Arnica montana is a perennial herbaceous, flowering plant, which has been used as a conventional therapeutic agent for thousands of years. This plant has been used predominantly to medicate various ailments such as backaches, sprains, superficial inflammations, injuries, wounds, and veterinary treatments (Garcia-Oliveira et al. 2021). The whole part of this plant is used as a herbal medication in homeopathy for treating 66 different pathological conditions (Kriplani et al. 2017). However, flower and root extracts have been utilized most frequently in the treatment of various health conditions. Extracts prepared from the root are applied externally on the bruises, rheumatic pains, sprains, and phlebitis to reduce the inflammations and as an immune system activator (Šutovská et al. 2014). Fresh as well as dried flower extracts are extensively used in modified form of tinctures, ointments, creams, gels as an immediate treatment of the sprains, bruises, contusions, and trauma pain in homeopathy medicine (Pieroni and Giusti 2009; Pljevljakušić et al. 2014; Vidic et al. 2016). The topical use of *Arnica* for abrasion and sequelae resulting from accidental injuries like hematoma, sprains, bruises, and dropsy owing to fractures, muscular pain and joint difficulties, insect bite irritation, and phlebitis has also been recognized by the German Commission E (Raza 2021).

A. montana constitutes a higher proportion of sesquiterpene lactones and is traditionally famous for its anti-inflammatory effects in most European countries (Lass et al. 2008). In British Columbia of Canada, veterinarians most commonly make the traditional use of herbal ointments as a protective band for wounds. An herbal ointment is prepared traditionally by mixing mashed flowers and leaves along with bee glue (Lans et al. 2007). People in South Africa use the leaves extract as a traditional healer to get relief from toothache and as a mouth cleanser (Ashu Agbor and Naidoo 2015). In the USA, dried flower is frequently consumed spice and has a traditional medicinal value as a diuretic, to induce sweating and as a stimulant (Sharma et al. 2016). Ongoing through different research articles, it was found that *Arnica* is typically considered safe in foods. This also validated from the Food and Drug Administration. It has been utilized in beverages: alcoholic and nonalcoholic, chilled desserts, confectionery, gelatins, and custards as a flavoring agent, in the form of hair tonic as anti-dandruff, fragrance, and other cosmetics. If significant doses of *Arnica* are consumed, the toxin helenalin present in it causes skin irritation and acute gastroenteritis resulting from internal bleeding of the intestinal tract. As a

result, *Arnica* extracts or decoctions are not suggested for its oral consumptions, while some expertise of homeopathy recommends highly reduced concentration. This diluted solution helps to reduce mild fever and treats cold, bronchitis, epilepsy, and sore throat (Denisow-Pietrzyk et al. 2019; Kawakami et al. 2011; Kouzi and Nuzum 2007; Šutovská et al. 2014).

4.3 Chemical Constituents

Arnica montana, an herbaceous perennial plant, mostly grows in the mountain region of Europe (Zucker 2008). Different parts of *A. montana* possess bioactive phytochemicals like flavonoids (FVs), caffeoyl quinic acid derivatives (CQAs), polysterol, phenolic compounds, and sesquiterpene lactones (SQLs) (Oana Teodora et al. 2016; Clauser et al. 2014). Due to these abundant bioactive phytochemicals, *A. montana* has important medicinal values.

The short-chain esters: sesquiterpene lactones, helenalin, and dihydro-helenalin are the main chemicals found in *Arnica* (Fig. 4.1). Helenalin comprises an endocyclic, unsaturated ketone (cyclopentenone), which gives hetero-Michael addition with thiols and act as an NF-kB singling which serves as an anti-inflammatory (Widen et al. 2017). Removing one of the two Michael acceptors of helenalin as compared with parent natural compounds, such as cyclopenten (producing 2,3-dihydrohelenalin) or -methylene-butyrolactone (generating 11,13-dihydrohelenalin; plenolin), dramatically reduces cytotoxicity (Lee et al. 1978). Some important phenolic compounds extracted from flowers are chlorogenic acid, 3,5-dicaffeoylquinic acid and 1-methoxyoxaloyl 3,5-dicaffeoylquinic acid which shows antioxidant activities (Clauser et al. 2014; Ganzera et al. 2008). Kimel et al. analyzed some active compounds from the group of phenolic acids such as derivatives of benzoic acid, p-hydroxybenzoic, protocatechuic, gallic, and vanillic; cinnamic acid derivatives, ferulic and caffeic; and phenolic acids of an ester nature, namely, caffeic acid esters of quinic acid (CQA), chlorogenic acid (5-O-CQA), cynarin (1,3-O-CQA), and isochlorogenic.

Flavonoids show antioxidant and antimicrobial activities. Flavonoid compounds belonging to the group of flavones are luteolin, luteolin 7-O-glucoside, apigenin, and apigenin 7-O-glucoside. Similarly, the group of flavonols are kaempferol, astragalin (kaempferol 3-Oglucoside), hyperoside (quercetin 3-O-galactoside), quercetin, isoquercetin (quercetin-3-O-glucoside), and isorhamnetin.

Cumene, 2,6-diisopropylanisole, decanal, and 1,2,2,3-tetramethylcyclopent-3-enol (Fig. 4.2) are major volatile compounds from the flower of the *Arnica montana* (Sugier et al. 2019). The essential oil of *A. montana* L. Achenes also known for the bioactive compounds consists of 20–23% monoterpene, (10%) sesquiterpene, and 7% aliphatic aldehyde as major constituents (Sugier et al. 2019). There are more than 40 chemical compounds including phenolic acid, organic acids, and fatty acids found in the essential oil of the root of *A. monata* (Petrova et al. 2015). Some major chemical constituents of the essential oil obtained from root and rhizome of

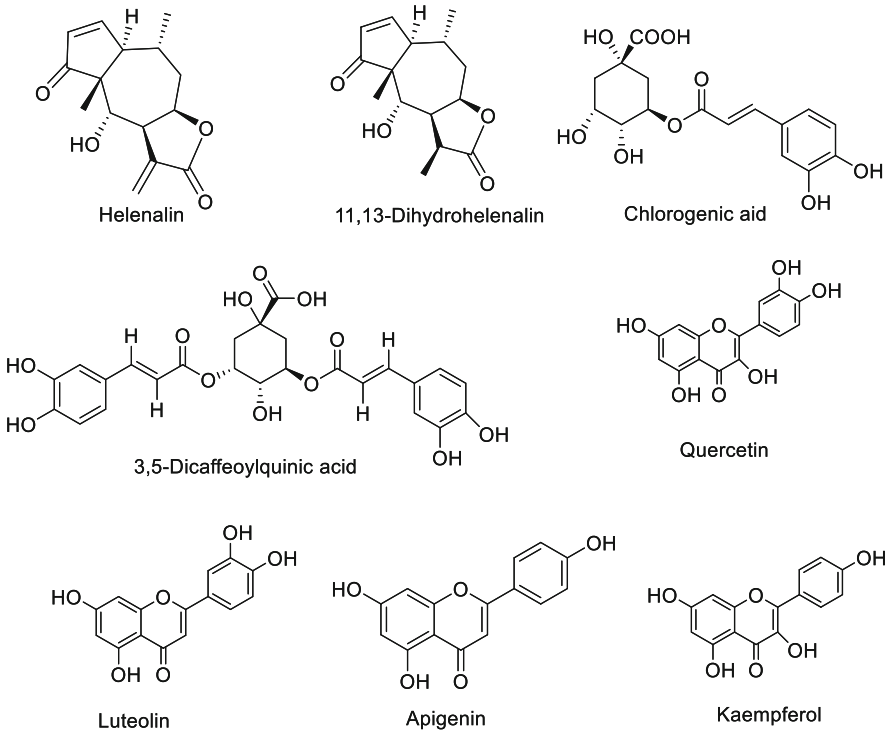

Fig. 4.1 Chemical compositions of lactones, phenols, and flavonoids in *Arnica montana*

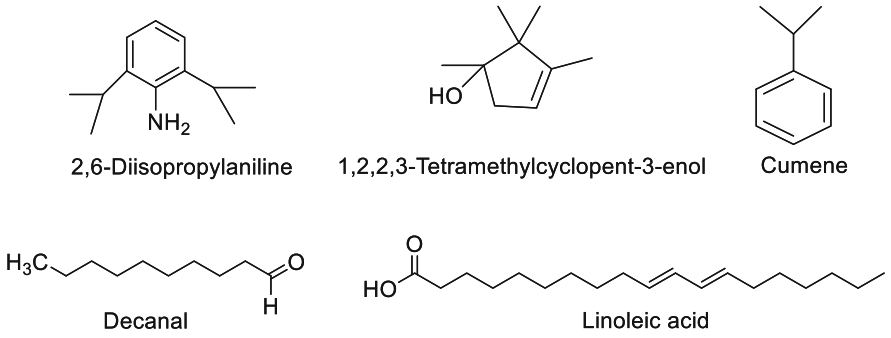

Fig. 4.2 Volatile chemical compounds of *Arnica montana* essential oil

A. monata are 2,5-dimethoxy-p-cymene, thymol methyl ether, p-methoxyheptanophenone, 2,6-diisopropylanisole, etc. (Pljevljakušić et al. 2012).

4.4 Pharmacological Activities

A. montana is a medicinally significant herb frequently used in pharmacy, homeopathy, and cosmetics. Different parts of plants are rich sources of chemical constituents and essential oils such as sesquiterpenes, terpenoids, sesquiterpene lactones, flavonoids, phenolic acid, and most particularly chlorogenic acids (Sugier et al. 2013). The presence of these chemical constituents mediates various pharmacological properties which includes anti-inflammatory, antioxidant, anti-cancerous, anti-hemorrhage, anti-osteoarthrities, antiplatelet, and immunomodulatory activities (Greinwald et al. 2022; Macêdo et al. 2004; Sugier et al. 2013).

4.4.1 Anti-inflammatory Activity

In 2008, an experiment was performed to evaluate the effect of phonophoresis along with *Arnica montana* on the acute inflammation induced in rat muscle. A 90-day-old Wistar male rat model was taken under study, and tibialis anterior muscle was surgically lesions to induce inflammation. Treatment was carried out in four different groups with 10 in each as a control group with no treatment, US group upon treatment with Ultrasound, US+A group treated with both US and *arnica* gel massage, and a group with only *arnica* gel. A 3-minute session treatment per day was initiated 24 h of lesions in each group for 3 days. Quantitative analysis of the isolated inflamed muscles showed a condensed mononuclear cells (macrophages) and light weight polymorphonuclear cells (neutrophils) in all groups than the control group. A histopathological study showed groups with the US acted as a pro-inflammation rather than anti-inflammation which might be due to the stimulatory effect of the US. This study finally revealed *arnica* gel is alone effective in the treatment of inflammations due to acute muscle lesions (Alfredo et al. 2009).

In 2009, phyto-medicine prepared from *A. montana* flowers was subjected to learn the mechanism that inhibits transcription factor AP-1 and NF-kB. This factor regulates the genes: MMP1 and MMP13. Bovine and human chondrocytes cells were taken for the experiment. Four different *Arnica* formulations were applied on MMP1 and MMP13 gene expression arisen from the induction of IL-1β by using real-time qPCR. An electrophoretic mobility shift binding assay was performed to study DNA binding activity of AP-1 and NF-kB. Both human and bovine chondrocytes were treated with 20 ng/mL IL-1β for 4 h to stimulate MMP1 and MMP13 gene expression. MMP1 and MMP13 expression levels in stimulated chondrocytes showed 67 and 213 fold greater, respectively, than in untreated cells. Treatment of different doses of *arnica* before the activation by IL-1β showed significantly decreased levels of MMP1 and MMP13 mRNA. The effect of the gene expression was dose-dependent. Among different formulations, central European *arnica* extract at concentrations of 0.2 and 0.5 μL/mL showed the most effective inhibitory effect. Similarly, AP-1 and NF-kB DNA binding activity was

inhibited by *Arnica* extract in dose-dependent manner. Among all, the European *Arnica* tincture showed the highest inhibitory activity at 5 μL/mL. Helenalin isobutyrate was taken as a positive control in both of the mechanisms. This study concluded that the degradation of MMP1 and MMP13 is an attractive mechanism for the treatment of inflammation due to osteoarthritis (Jäger et al. 2009). A similar type of study was carried out to evaluate the anti-inflammatory activity due to LPS stimulations in J774 murine macrophages. This study showed that *arnica* was effective in the reduction of iNOS ($P < 0.05$) and COX-2 ($P < 0.01$) protein level and inhibition in the production of IL-12(2.8 fold, $P < 0.001$) and inhibited nuclear translocation of NF-kB which are the main pro-inflammatory (Verma et al. 2010).

In 2020, another experiment was carried out to study the anti-inflammatory effect of the *A. montana* in skin burn mice induced by UVB radiation. This study was conducted on 25 male Swiss mice of 90 days old. Mice were enclosed in a polypropylene box with the controlled conditions of light/dark cycle of alternating 12 h. The study was carried out with division of mice into five groups: control group (no UVB + no treatment), vehicle group (no UVB + ointment without active principle), third, fourth, and fifth group with UVB radiations along with ointment without active, with active principle *Arnica*, and dexamethasone, respectively. UVB radiation was exposed for 20 h. After 16 h of treatments, mouse ear was further processed for the biochemical assays. Topical treatment of the *arnica* ointment reduced edema in mouse and myeloperoxidase activity induced by UVB radiations and inhibited marked inflammatory response of the NF-kB cytokine transcription factor. This study shows *Arnica* ointment ($p < 0.001$) as effective as positive control dexamethasone ($p < 0.05$) in treatment of the skin inflammation (da Silva Prade et al. 2020).

4.4.2 Anticancer Activity

Sugier et al. in 2019 evaluated the anticancer activity from essential oil of *A. montana* L. achenes. Human anaplastic astrocytoma MOGGCCM and glioblastoma multiforme T98G cell lines were chosen to study anticancer activity. The essential oil at varying concentrations (0, 0.5, 1, 2 μL/mL) was applied to cell lines. 0.5 μL/mL showed effective induction of cell death in MOGGCCM cell line as compared to T98G cell line. IC50 values also reveal the same case: 1.6 and 1.8 value for MOGGCCM cell line and 2.1 and 2.0 for T98G cell line. This study showed extreme proportion of 2, 5-dimethoxy-p-cymene in the essential oil which played an important role of anticancer potential against MOGGCCM and T98G cell line (Sugier et al. 2019).

Similarly, Sugier et al. in 2020 further reported the anticancer activity from essential oil of *A. montana. L.* roots and rhizomes. This study followed a similar procedure to the study conducted lately in 2019 (Sugier et al. 2019). Essential oil of rhizomes and roots at Various concentrations (0, 0.5, 1, 2 μL/mL) were subjected to MOGGCCM and T98G cell lines where 1 μL/mL showed efficient effect on

apoptosis of the cell line. At the same time, there is a low level effect of necrosis. Induced apoptosis at a level of 28.5–32.3% was more effective which revealed that chemical components such as 2,5-dimethoxy-p-cymene, 2,6-diisopropylanisole, thymol methyl ether, and p-methoxyheptanophenone were responsible for anticancer activity (Sugier et al. 2020).

4.4.3 Antioxidant Activity

In 2012, Craciunescu et al. evaluated the antioxidant activities of *A. montana* flower from ethanolic extract. Antioxidant activity was examined by using Trolox equivalent antioxidant capacity (TEAC), oxygen radical absorbance capacity (ORAC), and DPPH free radical assays. Obtained IC50 value of DPPH was 0.63 ± 0.07 mg/mL; TEAC and ORAC were 486.06 ± 20.63 μmol Trolox equivalents/g extract and 682.22 ± 17.32 μmol of Trolox equivalents/g extract. *Arnica* extracts were found to be rich in flavonoids and polyphenolic compounds which mediated antioxidant capacity (Craciunescu et al. 2012).

In 2016, Vidic et al. demonstrated the antioxidant capacity from essential oil of *A. montana* flower heads. Antioxidant potential was determined by using ABTS, DPPH, reducing power, and phosphomolybdenum assay while carvacrol, caryophyllene oxide (natural antioxidant), and BHT (synthetic antioxidant) as a standard reference. Its essential oil showed the highest value of DPPH (IC50 = 4.79 mg/mL) than standard carvacrol (IC50 = 14.38 mg/mL). Also, phosphomolybdenum assay showed better antioxidant potential 55.69 mg (AAE)/g equivalent to the DPPH method. The study showed antioxidant property is associated with the presence of fatty acids and phenolic compounds and their derivatives (Vidic et al. 2016).

4.4.4 Antimicrobial Activity

Recently, in 2021 Nieto-trujillo et al. demonstrated in vitro antibacterial potential of the methanolic extract of *A. montana* seed. Kirby-Bauer method was used to test against *S. aureus* (ATCC25923) and *E. coli* (ATCC25922) strains by using vancomycin(1 μg/disk) and chloramphenicol (1 μg/disk) as a positive control, respectively. The diluted fraction as negative control while sterile water was used as growth control. All the fractions (1–8 μg/disk) of extracts showed remarkable growth inhibition of the *E. coli* and *S. aureus*. 8 μg/disk for three different fractions (4 AM, 5 AM, and 6 AM) showed maximum inhibition percentage (14.48%, 16.31%, and 17.57%, respectively) of *E. coli*. The highest percentage of inhibition for *S. aureus* was revealed by 4 AM (16.8%) and 6 AM (20.48%) fractions. Three different fractions consisting of potent SMs: gallic acid, quercetin, verbascoside,

parthenolide, and sesquiterpene lactone contents are directly correlated with its antibacterial activity (Nieto-Trujillo et al. 2021).

4.4.5 Antiplatelet Activities

In 2015, Rywaniak et al. evaluated in vitro antiplatelet properties of the polyphenolic isolated from *A. montana* flowers. Healthy human blood was collected from the age group 35.7 ± 10.3 years. Blood incubated with 1% CellFix was used as a positive control and Flow cytometry was used to determine blood platelet viability. 7.5 and 15 mg/mL of *arnica* flower extract showed promising inhibitory action on ADP-stimulated platelet aggregations in blood and PRP and VASP phosphorylation without any toxic effect. This study showed that antiplatelet activity is due to the interaction of the polyphenolic compound of *Arnica* with the platelet surface membrane $P2Y_{12}$ receptor (Rywaniak et al. 2015).

4.4.6 Immunomodulatory and Wound Healing

In 2016, Marzotto et al. examined an in vitro model for evaluating the effect of the *A. montana* on its gene expression relating the wound healing mechanism. Interleukin-4 (IL-4) polarized THP-1 macrophage cell line was used for the analysis. Mother tincture of one centesimal dilution prepared in 30% ethanol and test was carried by incubating 24 h with 2, 3, 9, and 15 centesimal and control, respectively. The control solution used was a 100× diluted solution from the 1c standard *Arnica* solution. 8 week-old, wild-type C57BL/6 J mice were chosen to isolate macrophages from its bone marrow, and wound healing property was tested. The concentration of fibronectin rises up significantly with different centesimal *A. montana* dilution (13.9–39.6% with p value <0.05). This study revealed the healing mechanism of the wound was a bit faster in presence of *A. montana* (99.3 ± 0.1%) than control solvent (98.8 ± 0.7) in IL-4-induced cells. The recovery process was relatively efficient (30%) over control solvent. Also, concluded release of fibronectin is associated with the therapeutic role of wound repairing (Marzotto et al. 2016).

4.5 Clinical Studies

Clinical studies have been performed on *A. montana* aiming to act as a remedy for acute and chronic health problems. *A. montana* has been the source of extensive clinical trials, the researcher had made ample contrasting trial ointment showed repair and regression of postoperative edema and ecchymosis.

The double-blind placebo-controlled study, with 4-arm parallel group phase involved 570 patients. *Arnica* tincture spray (41.5 mg) was also tested in combination with hydroxyethyl salicylate (HES; 12.5 mg) as compared to *Arnica* (41.5 mg), HES (12.5 mg), and placebo for treatment of ankle joint distortion related pain. Combined application of *Arnica* and HES (4–5 times per day) in 50 patients showed immediate recovery. This was assessed by visual analogue scale (VAS). In conclusion, this research revealed that *Arnica* can work in conjunction with other drugs, such as HES, to alleviate pain associated with sprained ankle joint deformity (Kučera et al. 2011). In a 2-week double-blind randomized research, 16 healthy participants were given a 595-nm pulsed-dye laser to create 7-mm standard bruises on their upper inner arms, with contrasting results. When comparing VAS bruise ratings, 20% *Arnica* gel reduced bruising when compared to placebo and a gel containing 1% vitamin K and 0.3% retinol. But, there was no significant difference on comparing 5% vitamin K gel (Leu et al. 2010). *Arnica* cream administered immediately after completing calf raises and 24–48 h later failed to improve leg pain, mobility, or muscle tenderness when compared to placebo in a randomized double-blind trial including 53 participants (Adkison et al. 2010). Arnica 6D tablet, *Arnica* ointment, and placebo were used as research and control medications. Hand surgery (endoscopic carpal tunnel release) was diagnosed in 37 patients for 2 weeks as part of the inclusion criteria. In addition, topical *Arnica* along with homeopathic dilutions greatly minimized postoperative pain. The *Arnica*-treated group experienced a significant reduction in pain in contrast to the placebo group (Jeffrey and Belcher 2002).

Using prospective double-blind, randomized placebo-controlled trial trials conducted over a 20 month period with 55 patients, researchers found that the effect of two homeopathic remedies on postmastectomy seroma production was reduced when used in breast reconstructive surgery. Compared to 6.1–6.4 days, the drain removal time was reduced by 2.4 days in this study (Lotan et al. 2020). Clinical study on ecchymosis resulted after rhinoplastic surgery was carried out among 74 patients for 10 days. A randomized, placebo-controlled, and double-blinded fashion was conducted to design the study. The extent and intensity of postoperative ecchymosis in rhinoplasty surgery were reduced in this study (Chaiet and Marcus 2016). Similarly, the study on ecchymosis and edema found that local *Arnica* and mucopolysaccharide polysulfate cream treatments reduced ecchymosis and edema throughout the postoperative phase in 108 patients for 10 days. In open rhinoplastic surgery, mucopolysaccharide polysulfate ointment showed repair and regression of postoperative edema and ecchymosis (Simsek et al. 2016).

Thus, the prospective randomized double-blinded, randomized placebo method and open multicenter trials were performed in different patients in a controlled manner with homeopathy for effective outcomes.

4.6 Studies Related to Safety and Toxicity

However, dosing is not standardized throughout the products, resulting in differences in concentration levels (Cameron and Chrubasik 2013). Doses and dilutions were usually well-tolerated and employed with few patients experiencing adverse effects in clinical trials of *Arnica* from mild to moderate (Daane 2001). Topical creams should only be used on closed skin (Reddy et al. 2013). Although the use of homeopathic remedies is on the rise, these treatments are frequently seen as safe and risk-free by patients. The increasing and widespread use of alternative substances found in *A. montana* and materials in the treatment of skin diseases has been accompanied by heated debates between orthodox academic medicine, which is often portrayed as aggressive, toxic, harmful, and alternative medicine, which is represented as natural, bland, and free of side effects but is condemned as unscientific and ineffective (Reider et al. 2001). In clinical trials burning, reddening, itching, and urticaria were observed in the group receiving hydroxyethyl salicylate (Kučera et al. 2011). Racing hurt occurring as a cardiovascular event observed in both homeopathy and placebo groups (Cornu et al. 2010). Severe gastroenteritis ("Final Report on the Safety Assessment of Arnica Montana Extract and Arnica Montana," 2001), anxiety, rapid heart rate, muscle weakness, and mortality have been documented after consuming *A. montana* containing drugs ("Final Report on the Safety Assessment of Arnica Montana Extract and Arnica Montana," 2001). Even though homeopathy products and topical applications contain many toxic ingredients in *Arnica*, they are usually safe to use while breastfeeding but they should not be used on broken skin, as it can cause allergic skin reactions and cross-reactions in people who are allergic to these plants (Bethesda 2006).

The greater propensity of blood platelets to clump and induce cell damage owing to cytotoxic effects may both result in enhanced medium transparency (monitored as increased aggregation) in optical (turbidimetric) aggregation as a result of reduced impedance (resistance) detected in impedance (electrical) analysis, as well as whole blood aggregation, could be due to decreased platelet adherence and clumping on the electrodes or antiplatelet cytotoxic effects (Rywaniak et al. 2015).

4.7 Conclusions and Future Recommendations

Arnica montana is an aromatic herbaceous plant. It is used as a traditional remedy for various ailments, especially in European countries. It is used as an alternative treatment for various pathological conditions such as pain, stiffness, sprain, bruises, and rheumatoid arthritis. *A. montana* is rich in active biochemicals such as: sesquiterpene lactones, flavonoids, and fatty acids with therapeutic benefits possessing potent pharmacological properties including anti-inflammatory, anticancer, antioxidant, antimicrobial, antiplatelet, and anti-osteoarthritis drugs. Different clinical investigations are frequently conducted on homeopathic treatment. These studies

have shown that gel, pills, cream, ointments, and spray have promising pain-relieving effects. In an open multicenter trial, randomized double-blind, and placebo-controlled studied, the efficacy of *Arnica* on pain and postoperative recovery was assessed.

The chemical constituents present in roots, rhizomes, and leaves were affected by different ecology and climatic conditions. Sesquiterpene lactone is the main compound showing anti-inflammatory property. *A. montana* is used for topical formulation in the form of creams, ointments, and gels with 20–25% of this plant extract. Homeopathic practitioners recommend oral administration of a diluted solution of arnica extracts, but more studies are needed to confirm oral formulations of this plant extract. Helenalin is a toxic chemical compound showing various side effects. Therefore, researchers must focus on the toxicity level present in *A. montana* and the methods for the isolation of toxic compounds. If toxic compounds are isolated, it will be helpful for the preparation of oral herbal medication. *A. montana*, a medicinal plant, could be a source of new pharmaceuticals. Different sections of plants have medicinal effects but still, some portions of this plant are not investigated thoroughly. As the need for pharmaceuticals for various ailments grows, researchers should continue to look for novel and effective drugs through procedures that demonstrate a high level of medical value. Utilizing *A. montana*, which is found in several parts of the country, should be commercially farmed to aid in the industrialization and employment of residents, improving the country's economic status.

References

Adkison JD, Bauer DW, Chang T et al (2010) The effect of topical arnica on muscle pain. Ann Pharmacother 44(10):1579–1584. https://doi.org/10.1345/aph.1P071

Aiello N, Bontempo R, Vender C et al (2012) Morpho-quantitative and qualitative traits of Arnica montana L wild accessions of Trentino, Italy. Ind Crops Prod 40:199–203. https://linkinghub.elsevier.com/retrieve/pii/S0926669012001513

Alfredo PP, Anaruma CA, Pião AC et al (2009) Effects of phonophoresis with Arnica montana onto acute inflammatory process in rat skeletal muscles: an experimental study. Ultrasonics 49(4–5):466–471. https://doi.org/10.1016/j.ultras.2008.12.002

Anon (2001) Final report on the Safety assessment of Arnica montana extract and Arnica montana. Int J Toxicol 20(2):1–11. https://doi.org/10.1080/10915810160233712

Ashu Agbor M, Naidoo S (2015) Ethnomedicinal plants used by traditional healers to treat oral health problems in Cameroon. Evid Based Complement Alternat Med 2015:e649832. https://doi.org/10.1155/2015/649832

Bethesda (2006) Drug and Lactation Database (LactMed). National Library of Medicine (US). https://www.ncbi.nlm.nih.gov/pubmed/30000888

Cameron M, Chrubasik S (2013) Topical herbal therapies for treating osteoarthritis. Cochrane Database Syst Rev 2013:CD010538. https://doi.org/10.1002/14651858.CD010538

Chaiet SR, Marcus BC (2016) Perioperative Arnica montana for reduction of ecchymosis in rhinoplasty surgery. Ann Plast Surg 76(5):477–482. https://doi.org/10.1097/SAP.0000000000000312

Clauser M, Aiello N, Scartezzini F et al (2014) Differences in the chemical composition of Arnica montana flowers from wild populations of North Italy. Nat Prod Commun 9(1):3–6. https://doi.org/10.1177/1934578X1400900102

Cornu C, Joseph P, Gaillard S et al (2010) No effect of a homeopathic combination of *Arnica montana* and *Bryonia alba* on bleeding, inflammation, and ischaemia after aortic valve surgery. Br Clin Pharmacol 69(2):136–142. https://doi.org/10.1111/j.1365-2125.2009.03574.x

Craciunescu O, Constantin D, Gaspar A et al (2012) Evaluation of antioxidant and cytoprotective activities of Arnica montana L. and Artemisia absinthium L. ethanolic extracts. Chem Central J 6(1):97. https://doi.org/10.1186/1752-153X-6-97

da Silva Prade J, Bálsamo EC, Machado FR et al (2020) Anti-inflammatory effect of Arnica montana in a UVB radiation-induced skin-burn model in mice. Cutan Ocul Toxicol 39(2): 126–133. https://doi.org/10.1080/15569527.2020.1743998

Daane SP (2001) Potential for danger with Arnica Montana. Ann Plast Surg 46(3):349–350. https://doi.org/10.1097/00000637-200103000-00033

Denisow-Pietrzyk M, Pietrzyk L, Denisow B (2019) Asteraceae as a potential environmental factors of allergy. Environ Sci Pollut Res Int 26(7):6290–6300. https://doi.org/10.1007/s11356-019-04146-w

Ganzera M, Egger C, Zidorn C et al (2008) Quantitative analysis of flavonoids and phenolic acids in Arnica montana L. by micellar electrokinetic capillary chromatography. Anal Chim Acta 614(2):196–200. https://doi.org/10.1016/j.aca.2008.03.023

Garcia-Oliveira P, Barral M, Carpena M et al (2021) Traditional plants from Asteraceae family as potential candidates for functional food industry. Food Funct 12(7):2850–2873. https://doi.org/10.1039/D0FO03433A

Greinwald A, Hartmann M, Heilmann J et al (2022) Soil and vegetation drive Sesquiterpene lactone content and profile in Arnica montana L. flower heads from Apuseni-Mountains, Romania. Front Plant Sci 13:813939. https://doi.org/10.3389/fpls.2022.813939

Hollmann V, Donath T, Grammel F et al (2020) From nutrients to competition processes: habitat specific threats to Arnica montana L. populations in Hesse, Germany. PLoS One 15(5): e0233709. https://doi.org/10.1371/journal.pone.0233709

Iannitti T, Morales-Medina JC, Bellavite P et al (2016) Effectiveness and safety of Arnica montana in post-surgical setting, pain and inflammation. Am J Ther 23(1):e184. https://doi.org/10.1097/MJT.0000000000000036

Jäger C, Hrenn A, Zwingmann J et al (2009) Phytomedicines prepared from *Arnica* flowers inhibit the transcription factors AP-1 and NF-κB and modulate the activity of MMP1 and MMP13 in human and bovine chondrocytes. Plant Media 75912:1319–1325. https://doi.org/10.1055/s-0029-1185668

Jeffrey SLA, Belcher HJCR (2002) Use of Arnica to relieve pain after carpal-tunnel release surgery. Altern Ther Health Med 8(2):66–68. https://pubmed.ncbi.nlm.nih.gov/11892685/

Jürgens FM, Behrens M, Humpf HU et al (2022) In vitro metabolism of helenalin acetate and 11α,13-dihydrohelenalin acetate: natural Sesquiterpene lactones from arnica. Meta 12(1):88. https://doi.org/10.3390/metabo12010088

Kawakami AP, Sato C, Cardoso TN et al (2011) Inflammatory process modulation by homeopathic *Arnica montana* 6CH: the role of individual variation. Evid Based Contemp Altern Med 2011: 1–12. https://doi.org/10.1155/2011/917541

Kouzi SA, Nuzum DS (2007) Arnica for bruising and swelling. Am J Health Syst Pharm 64(23): 2434–2443. https://doi.org/10.2146/ajhp070155

Kriplani P, Guarve K, Baghael US (2017) *Arnica montana L.* – a plant of healing: Review. J Pharm Pharmacol 64(23):2434–2443. https://doi.org/10.2146/ajhp070155

Kučera M, Kolar P, Barna M, Kučera A, Hladiková M (2011) Arnica/hydroxyethyl salicylate combination spray for ankle distortion: a four-arm randomised double-blind study. Pain Res Treat 2011:365625. https://doi.org/10.1155/2011/365625

Lans C, Turner N, Khan T, Brauer G, Boepple W (2007) Ethnoveterinary medicines used for ruminants in British Columbia, Canada. J Ethnobiol Ethnomed 3(1):11. https://doi.org/10.1186/1746-4269-3-11

Lass C, Vocanson M, Wagner S, Schempp CM et al (2008) Anti-inflammatory and immune-regulatory mechanisms prevent contact hypersensitivity to *Arnica montana* L. Exp Dermatol 17(10):849–857. https://doi.org/10.1111/j.1600-0625.2008.00717.x

Lee KH, Ibuka T, Mar EC, Hall IH (1978) Antitumor agents. 31. Helenalin sym-dimethylethylenediamine reaction products and related derivatives. J Med Chem 21(7): 698–701. https://doi.org/10.1021/jm00205a022

Leu S, Havey J, White LE, Martin N, Yoo SS et al (2010) Accelerated resolution of laser-induced bruising with topical 20% arnica: a rater-blinded randomized controlled trial: topical treatments for bruising. Br J Dermatol 163(3):557–563. https://doi.org/10.1111/j.1365-2133.2010.09813.x

Lotan AM, Gronovich Y, Lysy I, Binenboym R et al (2020) Arnica Montana and Bellis perennis for seroma reduction following mastectomy and immediate breast reconstruction: randomized, double-blind, placebo- controlled trial. Eur J Plast Surg 43(3):285–294. https://doi.org/10.1007/s00238-019-01618-7

Macêdo SB, Ferreira LR, Perazzo FF, Tavares Carvalho JC (2004) Anti- inflammatory activity of *Arnica montana* 6cH: preclinical study in animals. Homeopathy 93(3):84–87. https://doi.org/10.1016/j.homp.2004.02.006

Maryna K, Trush K, Koscova J, Eftimová J (2019) Antimicrobial, antioxidant and some biochemical properties of arnica Montana L. Bull Problems Biol Med 3:268. https://doi.org/10.29254/2077-4214-2019-3-152-268-273

Marzotto M, Bonafini C, Olioso D, Baruzzi A et al (2016) *Arnica montana* stimulates extracellular matrix gene expression in a macrophage cell line differentiated to wound-healing phenotype. PLoS One 11(11):E0166340. https://doi.org/10.1371/journal.pone.0166340

Nieto-Trujillo A, Cruz-Sosa F, Luria-Pérez R, Gutiérrez-Rebolledo GA et al (2021) *Arnica montana* cell culture establishment, and assessment of its cytotoxic, antibacterial, α-amylase inhibitor, and antioxidant in vitro bioactivities. Plan Theory 10(11):2300. https://doi.org/10.3390/plants10112300

Oana Teodora A, Elena T, Lacon E, Cretu R et al (2016) Phytochemical screening and chromatographic fingerprint studies on ethanolic extracts of Arnica montana L. pp 53–60

Obón C, Rivera D, Verde A, Fajardo J et al (2012) Arnica: a multivariate analysis of the botany and ethnopharmacology of a medicinal plant complex in the Iberian Peninsula and the Balearic Islands. J Ethnopharmacol 144(1):44–56. https://doi.org/10.1016/j.jep.2012.08.024

Petrova M, Zayova E, Dincheva I, Badjakov I, Vlahova M (2015) Influence of carbon sources on growth and GC-MS based metabolite profiling of Arnica montana L. hairy roots. Turk J Biol 39(3):469–478. https://doi.org/10.3906/biy-1412-37

Pieroni A, Giusti ME (2009) Alpine ethnobotany in Italy: traditional knowledge of gastronomic and medicinal plants among the Occitan of the upper Varaita Valley, Piedmont. J Ethnobiol Ethnomed 5(1):32. https://doi.org/10.1186/1746-4269-5-32

Pljevljakušić D, Rančić D, Ristić M, Vujisić L, Radanović D, Dajić-Stevanović Z (2012) Rhizome and root yield of the cultivated Arnica montana L., chemical composition and histochemical localization of essential oil. Ind Crop Prod 39:177–189. https://doi.org/10.1016/j.indcrop.2012.02.030

Pljevljakušić D, Janković T, Jelačić S, Novaković M et al (2014) Morphological and chemical characterization of Arnica montana L. under different cultivation models. Ind Crop Prod 52: 233–244. https://doi.org/10.1016/j.indcrop.2013.10.035

Raza A (2021) Clinical efficacy of homeopathic remedy "Arnica montana": a systematic review. Int J Homeopathy Complement Altern Med 13:13

Reddy KK, Grossman L, Rogers GS (2013) Common complementary and alternative therapies with potential use in dermatologic surgery: risks and benefits. J Am Acad Dermatol 68(4):e127–e137. https://doi.org/10.1016/j.jaad.2011.06.030

Reider N, Komericki P, Hausen BM, Fritsch P, Aberer W (2001) The seamy side of natural medicines: contact sensitization to arnica (Arnica montana L.) and Marigold (Calendula officinalis L.): contact allergy to Arnica and Marigold. Contact Dermatitis 45(5):269–272. https://doi.org/10.1034/j.1600-0536.2001.450503.x

Rywaniak J, Luzak B, Podsedek A, Dudzinska D, Rozalski M, Watala C (2015) Comparison of cytotoxic and anti-platelet activities of polyphenolic extracts from Arnica flowers and Juglans regia husks. Platelets 26(2):168–176. https://doi.org/10.3109/09537104.2014.894970

Sharma S, Arif M, Nirala RK, Gupta R, Thakur SC (2016) Cumulative therapeutic effects of phytochemicals in *Arnica montana* flower extract alleviated collagen-induced arthritis: inhibition of both pro-inflammatory mediators and oxidative stress: anti-arthritis effects of *Arnica montana* flower extract. J Sci Food Agric 96(5):1500–1510. https://doi.org/10.1002/jsfa.7252

Simsek G, Sari E, Kilic R, Bayar Muluk N (2016) Topical application of Arnica and mucopolysaccharide polysulfate attenuates periorbital edema and ecchymosis in open rhinoplasty: a randomized controlled clinical study. Plast Reconstr Surg 137(3):530e–535e. https://doi.org/10.1097/01.prs.0000479967.94459.1c

Spitaler R, Winkler A, Lins I, Yanar S, Stuppner H, Zidorn C (2008) Altitudinal variation of phenolic contents in flowering heads of *Arnica montana* cv. ARBO: a 3-year comparison. J Chem Ecol 34(3):369–375. https://doi.org/10.1007/s10886-007-9407-x

Stanik N, Lampei C, Rosenthal G (2020) Summer aridity rather than management shapes fitness-related functional traits of the threatened mountain plant *Arnica montana*. Ecol Evol 10(11): 5069–5078. https://doi.org/10.1002/ece3.6259

Sugier D, Sugier P, Gawalik-Dziki U (2013) Propagation and introduction of *Arnica montana L.* into cultivation: a step to reduce the pressure on endangered and high-valued medicinal plant species. ScientificWorldJournal 2013:e414363. https://doi.org/10.1155/2013/414363

Sugier D, Sugier P, Jakubowicz-Gil J, Winiarczyk K, Kowalski R (2019) Essential oil from *Arnica montana L.* achenes: chemical characteristics and anticancer activity. Molecules 24(22):4158. https://doi.org/10.3390/molecules24224158

Sugier P, Jakubowicz-Gil J, Sugier D, Kowalski R, Gawlik-Dziki U, Kolodziej B, Dziki D (2020) Chemical characteristics and anticancer activity of essential oil from *Arnica montana L.* rhizomes and roots. Molecules 25(6):1284. https://doi.org/10.3390/molecules25061284

Šutovská M, Capek P, Kočmalová M, Pawlaczyk I, Zaczyńska E et al (2014) Characterization and pharmacodynamic properties of *Arnica montana* complex. Int J Biol Macromol 69:214–221. https://doi.org/10.1016/j.ijbiomac.2014.05.051

Verma N, Tripathi SK, Sahu D, Das HP, Das RH (2010) Evaluation of inhibitory activities of plant extracts on production of LPS-stimulated pro-inflammatory mediators in J774 murine macrophages. Mol Cell Biochem 336(1–2):127–135. https://doi.org/10.1007/s11010-009-0263-6

Vidic D, Ćavar Zeljković S, Dizdar M, Maksimović M (2016) Essential oil composition and antioxidant activity of four Asteraceae species from Bosnia. J Essent Oil Res 28(5):445–457. https://doi.org/10.1080/10412905.2016.1150216

Widen JC, Kempema AM, Villalta PW, Harki DA (2017) Targeting NF-κB p65 with a helenalin inspired Bis-electrophile. ACS Chem Biol 12(1):102–113. https://doi.org/10.1021/acschembio.6b00751

Zucker L (2008) Chapter 6—Arnica. In: Deutsch JE, Anderson EZ (eds) Complementary therapies for physical therapy. W.B. Saunders, Philadelphia, PA, pp 75–83. https://doi.org/10.1016/B978-072160111-3.50012-9