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Eksplorasi Potensi Terapeutik *Portulaca oleracea* dalam Penanganan Acute Mountain Sickness

Exploring Portulaca oleracea: Potential Therapeutic Role in Acute Mountain Sickness

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Abstrak. Mendaki gunung telah menjadi aktivitas populer secara global, namun kegiatan ini memiliki risiko seperti *Acute Mountain Sickness* (AMS) atau Penyakit Gunung Akut, yang ditandai dengan gejala seperti sakit kepala, mual, dan kelelahan. Stres oksidatif dan peradangan akibat hipoksia merupakan faktor utama penyebab AMS. Meskipun pengobatan konvensional seperti acetazolamid banyak digunakan, pengobatan alami seperti *Portulaca oleracea* (krokot) menawarkan alternatif yang menjanjikan karena ketersediaannya dan potensi terapeutiknya. Studi ini menyelidiki sifat farmakologis *Portulaca oleracea* dan potensi perannya dalam mencegah atau mengurangi gejala AMS. Tinjauan naratif dilakukan dengan menggunakan basis data PubMed, ScienceDirect, dan Google Scholar. Kata kunci seperti "*Portulaca oleracea*," "*bioactive compounds*," dan "*Acute Mountain Sickness*" digunakan dalam pencarian. Studi yang membahas efek antioksidan, antiinflamasi, antihipoksia, dan antiangiogenik yang relevan dengan AMS disertakan. *P. oleracea* mengandung senyawa bioaktif seperti flavonoid, alkaloid, dan asam organik yang menunjukkan sifat antioksidan, antiinflamasi, dan antihipoksia. Ekstrak etanolnya (EEPO) menunjukkan efek neuroprotektif, dengan memodulasi ekspresi eritropoietin dan mempertahankan kadar ATP dalam kondisi hipoksia. Meskipun belum ada uji klinis pada manusia yang secara langsung mengaitkan *P. oleracea* dengan AMS, efek farmakologisnya sesuai dengan patofisiologi AMS, khususnya dalam mengurangi stres oksidatif dan peradangan. *P. oleracea* merupakan pengobatan alami yang menjanjikan untuk AMS dan memiliki implikasi signifikan dalam bidang *wellness and medical tourism*. Penelitian lanjutan, termasuk studi *in silico* (misalnya *molecular docking* dan *network pharmacology*) serta uji klinis, diperlukan untuk memahami sepenuhnya potensi terapeutiknya. Temuan ini menyoroti nilainya sebagai solusi yang mudah diakses dan berkelanjutan dalam pengobatan ketinggian dan wisata kesehatan.

Kata Kunci: Eksplorasi, *Portulaca oleracea*, *Acute Mountain Sickness*

Abstract. *Mountain hiking has become a popular global activity, but it poses risks such as Acute Mountain Sickness (AMS), characterized by symptoms like headaches, nausea, and fatigue. Hypoxia-induced oxidative stress and inflammation are key contributors to AMS. While conventional treatments like acetazolamide are widely used, natural remedies such as Portulaca oleracea (purslane or krokot) offer promising alternatives due to their accessibility and therapeutic potential. This study investigates the pharmacological properties of Portulaca oleracea and its potential role in preventing or mitigating AMS symptoms. A narrative review was conducted using PubMed, ScienceDirect, and Google Scholar. Keywords such as "Portulaca oleracea," "bioactive compounds," and "Acute Mountain Sickness" were applied. Studies focusing on antioxidant, anti-inflammatory, antihypoxic, and anti-angiogenic effects relevant to AMS were included. P. oleracea contains bioactive compounds like flavonoids, alkaloids, and organic acids, demonstrating antioxidant, anti-inflammatory, and antihypoxic properties. Ethanol extracts (EEPO) showed neuroprotective effects, modulating erythropoietin expression and maintaining ATP levels under hypoxic conditions. While no human trials directly link P. oleracea to AMS, its pharmacological effects align with AMS pathophysiology, particularly in reducing oxidative stress and inflammation. P. oleracea is a promising natural remedy for AMS, with significant implications for medical and wellness tourism. Future research, including in silico studies (e.g., molecular docking, network pharmacology) and clinical trials, is essential to fully understand its therapeutic potential. These findings highlight its value as an accessible, sustainable solution in altitude medicine and health tourism.*

Keywords: Exploration, Portulaca oleracea, Acute Mountain Sickness

INTRODUCTION

Mountain climbing or hiking has become an increasingly popular recreational activity globally and in Indonesia in recent decades. The desire to reconnect with nature and escape urban life drives many climbers. Beyond adventure, it is seen as a means to improve physical and mental health while fostering a deeper bond with nature. Globally, nearly 1,2 million tourists visited Nepal in 2019, with 171.937 engaging in trekking.[1] Africa's Mount Kilimanjaro hosted over 47.000 climbers in 2018, while Europe's Alps attract over 40 million visitors annually, and globally recording 400 million skier days across 2,000 resorts in 80+ countries.[2,3] In Indonesia, the Indonesian Mountain Guide Association (APGI) reported 150,000 international and 3 million domestic climbers in 2020, with this number tripling by 2023.[4] Mountain climbing's global appeal underscores its dual role as a recreational pursuit and a means to promote well-being.

The popularity of mountain climbing has surged, driven by social media trends and the "*fear of missing out*" (FOMO). Unfortunately, many climbers lack the physical and mental preparation necessary to face high-altitude environments. This increases their vulnerability to high-altitude illness (HAI), which includes Acute Mountain Sickness (AMS), and the severe forms are high-altitude pulmonary edema (HAPE), and high-altitude cerebral edema (HACE). AMS, the most common form, causes symptoms like headaches, nausea, and fatigue, and may escalate to life-threatening complications without timely intervention. The risk of AMS grows with higher altitudes and rapid ascents, underscoring the importance of prevention strategies.

To mitigate the risks of AMS, exploring effective preventive measures is essential. While conventional treatments like acetazolamide are commonly used, natural remedies are gaining attention due to their accessibility and fewer side effects.[5] Traditional medicine offers several natural remedies for AMS, derived from plants such as *Rhadiola*, *Ginkgo biloba*, *Tibetan turnip*, and *Portulaca oleracea* (purslane).[6,7] Unlike many exotic herbs, *Portulaca oleracea* is abundant in Indonesia, making it a viable and accessible option.[8–11] This plant, commonly used as food in Asia and other regions, contains bioactive compounds such as alkaloids and flavonoids, which hold medicinal potential.[12,13] Its widespread availability highlights purslane as a promising candidate for further exploration in AMS prevention efforts. This review aims to explore the potential of *Portulaca oleracea* in curing AMS, focusing on medicinal properties. As wellness tourism continues to grow, particularly in mountain climbing destinations, natural remedies like purslane may offer a viable alternative to conventional treatments. By examining the available evidence, this study seeks to highlight the plant's potential role in enhancing the overall experience of medical tourism, particularly in regions with high-altitude trekking, where AMS prevention is crucial.

METHODS

This narrative review synthesizes studies retrieved from PubMed and Science Direct for English language studies, and Google Scholar for Indonesian language studies. Keywords used include "*Portulaca oleracea*" (and its synonyms krokot or purslane), "therapeutic effect", "bioactive compound", and "Acute Mountain Sickness." Boolean operations were used to combine the keywords. Articles without full-text access, gray literature, studies published in languages other than Indonesian or English, and research not focusing on secondary metabolites of *Portulaca oleracea* were excluded. The results and discussion will focus on three main aspects: the pathogenesis of Acute Mountain Sickness (AMS), the pharmacological properties of *Portulaca oleracea* that may inhibit AMS pathogenesis, and clinical or preclinical studies linking the plant's pharmacological effects to AMS prevention or treatment.

RESULTS AND DISCUSSIONS

1) Pathogenesis of Acute Mountain Sickness

In a clinical context, Luks *et al*.[14] states an individual is considered to have Acute Mountain Sickness (AMS) if they experience a headache accompanied by one or more additional symptoms, such as nausea, vomiting, fatigue, or persistent dizziness following an ascent to an altitude above 2300 meters. The diagnosis is based on self-reported symptoms, without any characteristic physical findings or laboratory tests. Neurological examination and the individual's mental status must be within normal limits; otherwise, alternative diagnoses, such as High-Altitude Cerebral Edema (HACE), should be considered. Altitudes above 1,500 meters are classified as highlands and categorized based on their effects on the human body. High Altitudes (1,500–3,500 meter) often result in altitude sickness, particularly during rapid ascents above 2,500 meters, causing symptoms like reduced physical performance, increased ventilation rates, and slight arterial oxygen saturation (SaO2) decline. Arterial oxygen partial pressure (PaO2) at this level ranges between 55–75 mmHg. At Very High Altitudes (3,500–5,500 meter), severe altitude sickness is more prevalent, with SaO2 dropping to 75–85% and PaO2 to 40–60 mmHg, increasing the risk of extreme hypoxia during sleep or physical activity. In Extreme Altitudes (5,500–8,850 meter), physiological functions significantly deteriorate, surpassing the body's acclimatization capacity. Rapid ascents frequently lead to severe conditions, as SaO2 falls to 58–75% and PaO2 to 28–40 mmHg.[15]

The primary harmful effect at high altitudes is the reduction in oxygen partial pressure (pO2) due to decreasing barometric pressure, rather than hypobaria or other environmental factors. This poses acute risks for unacclimatized individuals, particularly at higher elevations. Hypoxia triggers a range of physiological and cellular responses to maintain tissue oxygenation, but excessive responses in some individuals can lead to altitude-related illnesses (HAI). Acute exposure to high altitudes activates the sympathetic nervous system, increasing heart rate, cardiac output, and ventilation.[16] Hyperventilation, driven by the hypoxic ventilatory response (HVR), results in low carbon dioxide levels (hypocapnia) and respiratory alkalosis, followed by renal bicarbonate excretion.[17] Unlike peripheral vasodilation, hypoxia induces pulmonary vasoconstriction and raises pulmonary arterial pressure. At the cellular level, hypoxia-inducible factors (HIF) stabilize, promoting the expression of genes like erythropoietin (EPO) and vascular endothelial growth factor (VEGF) to support erythropoiesis and angiogenesis, while excess reactive oxygen species (ROS) production can cause oxidative stress and inflammation.[16,18]

Inadequate acclimatization, rapid ascent, or individual susceptibility may lead to conditions like acute mountain sickness (AMS) or high-altitude cerebral edema (HACE) and high-altitude pulmonary edema (HAPE). AMS symptoms, such as headaches, arise from cerebral vasodilation, increased blood flow, and mild cytotoxic edema, driven by reduced Na+/K+-ATPase activity and ROS production.[16] Severe cases involve increased intracranial pressure, vascular permeability, and blood-brain barrier disruption due to HIF and VEGF activity, resulting in vasogenic edema and HACE. Proper acclimatization helps the body adapt to low oxygen environments, mitigating these risks.

Based on the pathogenesis of AMS (Picture 1), The pharmacological properties required to address Acute Mountain Sickness (AMS), in common form or severe form, include antioxidant, anti-inflammatory, antihypoxic, and anti-angiogenic effects.[15]

- Antioxidant Effects: These are necessary to counteract the increased production of reactive oxygen species (ROS) that occur at high altitudes, which contribute to oxidative stress and cellular damage.
- Anti-inflammatory Effects: Anti-inflammatory properties are required to inhibit inflammatory mediators, such as cytokines, which play a role in the inflammatory response triggered by hypoxia.
- Antihypoxic Effects: These address the problem of hypoxemia to prevent tissue hypoxia, ensuring adequate oxygen delivery and utilization by cells and tissues. Anti-angiogenic/ VEGF inhibitor Effects: These are needed to counteract the effects of vascular endothelial growth factor (VEGF), which can lead to increased vascular permeability and contribute to the development of edema.

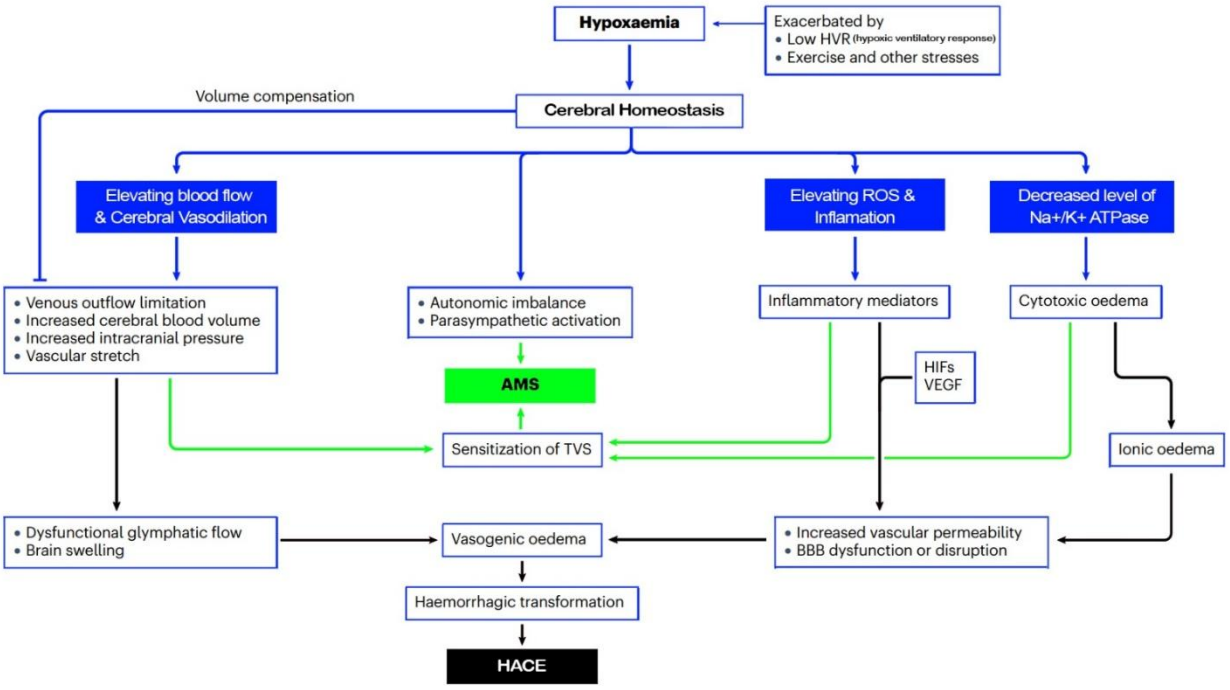

Figure 1. Summary of AMS Pathogenesis[15]

Footnote: ROS: reactive oxygen species; HIF: hypoxia-inducible factors (HIF); VEGF: vascular endothelial growth factor; BBB: blood-brain barrier; AMS: Acute Mountain Sickness; HACE: High Altitude Cerebral Edema; TVS: Trigeminal Vascular System

2) Therapeutic Effects of *Portulaca oleracea*

Based on the LC–MS/MS testing conducted by Nemzer *et al*. 184 compounds from *Portulaca oleracea* were identified. Among the 184 compounds identified through LC-MS/MS analysis—including phenolic acids, organic acids, flavonoids, alkaloids, and betanin—over 80 exhibited more than double the abundance in wild purslane compared to the cultivated variety.[19] The chromatographic analysis in the study identified seven compounds with the highest peak intensities: 1) Malic acid (m/z 133.0130), 2) Citric acid (m/z 191.0186), 3) Dihydroxybenzoic acid-hexoside (m/z 315.0714), 4)Dihydroxybenzaldehyde (m/z 137.0231), 5) Dihydroxybenzoic acid-pentoside (m/z 285.0609), 6) Coumaroylglucaric acid (m/z 355.0663), and 7) Feruloylmalic acid (m/z 309.0608).[19] That study reveals several bioactive compounds in *Portulaca oleracea*, including organic acids like malic and citric acids, hydroxybenzoic acid derivatives, and esterified hydroxycinnamic acids. These compounds, formed through esterification, show bioactivity in other plants, such as contributing to disease resistance and anti-inflammatory effects. The study also highlights

antioxidant alkaloids, like oleraceins, and flavonoids such as quercetin and kaempferol. Although portulacanones A–D were not identified, the findings underscore the diverse therapeutic potential of *P. oleracea*.[19]

Additionally, based on a search in the Google Scholar, PubMed, and Science Direct databases, *Portulaca oleracea* exhibits various therapeutic effects, which are presented in table 1. and categorized according to their therapeutic properties. In the table 1. therapeutic effects are categorized as "related" to Acute Mountain Sickness (AMS) if the research specifically investigates the four therapeutic effects previously outlined: antioxidant, anti-inflammatory, antihypoxic, and anti-angiogenic effects. The category "maybe" is applied if the study indicates therapeutic effects corresponding to these four aspects, along with additional effects that are not directly related. Finally, therapeutic effects are classified as "unrelated" if they do not fall within the aforementioned four categories.

The therapeutic effects of *Portulaca oleracea* vary across different studies, with potential benefits for several health conditions. The primary categories of therapeutic effects highlighted in the studies include:

1) Antioxidants: Several studies emphasize the antioxidant properties of *P. oleracea*, particularly in the reduction of oxidative stress markers such as malondialdehyde (MDA) and reactive oxygen species (ROS), while boosting antioxidant enzymes like superoxide dismutase (SOD) and catalase (CAT).[20–32] This effect has been observed in models related to Acute Mountain Sickness (AMS), supporting its potential use in alleviating oxidative damage in climbers.
2) Anti-inflammatory: Many studies point to the anti-inflammatory properties of *P. oleracea*, which reduce inflammatory markers like TNF-α, IL-6, IL-1β, and other cytokines.[21,22,24,26,31–44] These effects have been observed in various conditions, including ulcerative colitis, diabetes, and skin disorders, and may contribute to reducing inflammation related to AMS.
3) Anti-obesity and anti-diabetic: *P. oleracea* has been shown to have effects on insulin sensitivity, glucose uptake, and weight regulation, suggesting its potential role in managing obesity and diabetes, although this may not directly relate to AMS.[22,32,45]
4) Immunomodulatory: Several studies highlight the ability of *P. oleracea* to modulate immune responses, enhancing phagocytic activity, lymphocyte proliferation, and gut microbiota regulation.[37–40,42,46,47] These effects in some conditions may be relevant to the immune adaptations needed during high-altitude exposure.
5) Wound healing and tissue repair: There is also evidence supporting the role of *P. oleracea* in promoting tissue repair and wound healing, with implications for recovery after physical exertion in mountainous environments.[23,33]
6) Neuroprotective and cognitive enhancement: Studies on cognitive function and aging suggest that *P. oleracea* may have neuroprotective effects, improving cognition and reducing oxidative stress in the brain, which may indirectly benefit individuals experiencing cognitive fatigue at high altitudes.[52]
7) Neuroprotective and cognitive enhancement: Studies on cognitive function and aging suggest that *P. oleracea* may have neuroprotective effects, improving cognition and reducing oxidative stress in the brain, which may indirectly benefit individuals experiencing cognitive fatigue at high altitudes.[52]

Although the effects related to AMS are not universally established across all studies, the evidence suggests that its antioxidant and anti-inflammatory properties are particularly promising for mitigating the physiological stresses associated with high-altitude exposure.

3) Experimental & Observational studies related to *Portulaca oleracea* and AMS

Based on searches conducted in databases such as Google Scholar, PubMed, and ScienceDirect, covering a broader range of publication years, no study has specifically addressed the relationship between *Portulaca oleracea* and Acute Mountain Sickness. However, only one study by Yue *et al*. investigated *Portulaca oleracea* in rats to examine its therapeutic effects related to the severe form of Acute Mountain Sickness, which is High Altitude Pulmonary Edema (HAPE).[54] Additionally, two studies explored the antihypoxic effects of *Portulaca oleracea*, as hypoxia is one of key factor in the pathogenesis of Acute Mountain Sickness.[55,56]

The study by Yue *et al*.[54] demonstrated the protective effects of the ethanol extract of *Portulaca oleracea* (EEPO) against hypoxia-induced pulmonary edema. This condition is analogous to severe AMS symptoms like High Altitude Pulmonary Edema (HAPE). The study identified mechanisms such as reduced vascular leakage, decreased oxidative stress, and inhibition of proinflammatory cytokine expression. These findings align with the pathophysiological mechanisms of AMS, where hypoxia leads to endothelial dysfunction and inflammation. The observed dose-dependent efficacy of EEPO in reducing edema and oxidative stress underscores its therapeutic potential for altitude-related hypoxic conditions.[54]

Table 1. Therapeutic Effects of *Portulaca oleracea*

No	References	Extracts/ Components	Medicinal Parts	Doses	Study Model	Core mechanism/Result	Therapeutic effects category	Effects Related to AMS
1	Mashhadi et al.20	Hydroethanolic extract & α-linolenic acid (ALA) of P. oleracea	Aerial part	160 µg/ml Extract & 15&45 µg/ml ALA	PHA-stimulated lymphocytes & Non stimulated lymphocytes	↓ nitric oxide (NO) & malondialdehyde (MDA); ↑ thiol, catalase (CAT), superoxide dismutase (SOD).	Antioxidants	Yes
2	Park & Han45	HM-chromanone (extracted from Portulaca oleracea)	Aerial part	15 µM and 30 µM	L6 rat skeletal muscle cells (used to induce insulin resistance by palmitate treatment).	↑ pAMPK, ↓ mTOR/S6K1, ↓ IRS-1 phosphorylation, ↑ GLUT4, ↑ glucose uptake	Anti-obesity, anti-diabetic,	No
3	Di Cagno et al.21	Fermented P. oleracea juice (fermented with Lactobacillus species)	Aerial part		In vitro model using Caco-2 cell line	↑ Total antioxidant capacity (DPPH, ABTS, FRAP), ↓ Pro-inflammatory mediators (PGE2, NO), ↓ Intracellular ROS, ↑ Intestinal barrier function (TEER)	Anti-inflammatory, Antioxidant, Intestinal protection	Maybe
4	Rakhshandeh et al. 22	P. oleracea extract	Whole plant	100 & 300 mg/kg/ daily	Male rats streptozotocin-induced type I diabetes model	↓ Glucose levels; ↓ MDA, TGF-1, TNF-α; ↑ Seminiferous tubule diameter, sperm count, motility, LH, testosterone, VEGF, SOD activity.	Antidiabetic, Anti-inflammatory, Antioxidant, Fertility restoration	Maybe
5	Stoyanova et al.23	P. oleracea extract obtained by supercritical CO2	Whole plant		Electrospun PLA/ P. oleracea fibers; In vitro tests with normal mouse fibroblasts	Strong antioxidant activity, good mechanical properties, biocompatibility (promotes fibroblast adhesion, attachment, and proliferation)	Antioxidants, Antimicrobial, Wound healing	Maybe
6	Guo et al.33	Hydroalcoholic extract (P) & aqueous phase fraction (PD)	Aerial part		In vitro: HUVEC cells (viability, migration, tube formation) In vivo: DTPI rat model (vascularization, iron accumulation, wound healing)	In vitro: ↑ HUVEC viability, migration, tube formation (P, PD). In vivo: ↑ new blood vessels, VEGF-A; ↓ muscle iron (ICP-MS, Perls' staining); ↓ re-epithelization time, inflammatory infiltration; ↑ collagen deposition.	Wound healing, anti-inflammatory, anti-iron accumulation, revascularization, and tissue repair	Maybe
7	Oh et al.24	Solvent-fractionated extracts, 85% aq. MeOH fraction, Portulacanone A (PA), Portulacanon D (PD)	Aerial part		In vitro (UVB-stressed human keratinocytes)	↓ ROS, ↑ SOD-1 & HO-1 (via Nrf-2); ↓ MMPs; ↑ type I procollagen production; PA & PD inhibited MMP-1 secretion & increased type I procollagen production	Anti-photoaging, Antioxidants, Anti-inflammatory	Maybe

No	References	Extracts/ Components	Medicinal Parts	Doses	Study Model	Core mechanism/Result	Therapeutic effects category	Effects Related to AMS
8	Kim et al.34	Ethyl acetate (EtOAc) & Ethanol (EtOH) extracts; cis-N-feruloyl-3'-methoxytyramine, trans-n-feruloyltyramine, Portulacanone C	Aerial part	200 & 500 mg/kg (in vivo)	In vitro (LPS-induced RAW264.7 macrophages), In vivo (DSS-induced ulcerative colitis in ICR mice)	↓ Pro-inflammatory cytokines (TNF-α, IL-6, IL-1β); ↓ ERK, JNK, p38 phosphorylation; cis-N-feruloyl-3'-methoxytyramine had strongest effect on preventing DSS-induced IBD	Anti inflammatory, Inflammatory bowel disease (IBD) treatment	Maybe
9	He et al.35	PO extract; Myricetin (Myr)	Aerial part		In vitro (Free fatty acids-induced hepatocytes, Lipopolysaccharide-induced macrophages), In vivo (Methionine choline deficiency diet-induced NASH in mice)	↓ PTGS2, ↓ lipid droplets, regulates lipid genes (FASN, CPT1a, ACC1), ↓ TNF-α, IL-6, IL-1β, Myricetin inhibits PTGS2	Anti-inflammatory, Hepatoprotective, Treatment of Nonalcoholic Steatohepatitis (NASH)	Maybe
10	Chen et al.25	Ethanol, acetone, ethyl acetate, chloroform, n-hexane extracts; Quercetin, rosmarinic acid, kaempferol, chlorogenic acid, p-coumaric acid, caffeic acid, trans-ferulic.	Whole plant		In vitro assays	↓ radicals, ↓ tyrosinase & α-glucosidase activity	Antioxidants, Anti-tyrosinase, Anti-α-glucosidase	Maybe
11	Shanker & Debnath26	Water, ethanol, methanol extracts; Omega-3 fatty acids (α-linolenic acid - ALA), polyphenols	Whole plant		In vitro assays for total polyphenol content, antiradical activity, rehydration ratio; Comparison of different drying methods (microwave, tray, vacuum, low temperature low humidity, infrared)	Vacuum drying → ↑ ALA, polyphenols, antiradical activity, rehydration ratio	Antioxidant, Anti-inflammatory, Omega-3 fatty acid source	Maybe

No	References	Extracts/ Components	Medicinal Parts	Doses	Study Model	Core mechanism/Result	Therapeutic effects category	Effects Related to AMS
12	Fu et al. 36	15 water-soluble alkaloids	Fresh herbs	10 μM	RAW 264.7 macrophages, LPS-induced inflammation	↓ IL-6, NO levels in LPS-stimulated macrophages	Anti-inflammatory	Yes
13	Liu et al.48	50% EtOH fraction, Portulacaside B (6a), Epiportulacaside B (6b), Dihydrohomo-isoflavonoids (1–8)	Aerial part		HepG2 human liver cancer cells induced by N-acetyl-p-aminophenol (APAP), RAW 264.7 macrophages	↑ Survival rate (40% to 51.2%) in HepG2 cells, ↓ NO production in RAW 264.7 (46.8% inhibition)	Hepatoprotective, Anti-inflammatory	Maybe
14	Cannavacciuolo et al.37	Lipid-enriched fractions (100ACN-POL and 100ACN-POS)	Aerial part	20 μg/ml	In vitro reporter gene assays (NF-kB, PPAR-ɣ, Nrf2 activation)	↓ TNF-α-induced NF-kB (30-40%↓); ↑ PPAR-ɣ & Nrf2	Anti-inflammatory, Immuno-modulatory	Maybe
15	Yang et al.38	Polysaccharide of P. oleracea (POL-P)			In silico (network-based computational analysis, molecular docking), in vivo (UC mice model)	In silico: Binding of POL-P to TLR4; ↓ TLR4, MyD88, NF-κB expression in UC mice; Inhibition of TLR4 pathway	Anti-inflammatory, Immuno-modulatory	Maybe
16	Tao et al.49	Polysaccharide fraction (VPOP3)	Aerial part		In vitro (cell studies), In vivo (zebrafish model)	↓ ROS & lipid peroxidation; ↓ caspase-3 & Bax, ↑ Bcl-2); ↓ MITF & TYR.	Anti-photoaging, Anti-melanogenesis, Skin protection	No
17	Yi et al.50	Portulaca oleracea extract (POE)	Whole plant		Mouse model of colorectal cancer (CRC) induced by Azoxymethane (AOM) and dextransodiumsulfate (DSS)	↓ CRC development, ↓ gut microbiota imbalance, ↓ c-Myc & cyclin D1, ↓ Wnt/β-catenin pathway.	Anticancer, Wnt/β-catenin pathway modulation, CRC prevention/ treatment	No
18	Zhao et al.40	PO and fermented PO (FPO)	Whole plant	20 mg/mL	2,4-dinitrofluorobenzene-induced AD mouse model	↓ mast cell infiltration, ↓ IgE, histamine (HIS), and TSLP, ↓ inflammatory cytokines (TNF-α, IFN-γ, IL-4), ↑ filaggrin, ↓ NF-κB pathway (TNF-α, IKKα, p-IKKα, p-NF-κB, p-IκBα)	Anti-inflammatory, Immuno-modulatory, Skin barrier restoration,	Maybe

No	References	Extracts/ Components	Medicinal Parts	Doses	Study Model	Core mechanism/Result	Therapeutic effects category	Effects Related to AMS
19	Yue et al. 27	Viscozyme-assisted polysaccharide (VPOP1)	Whole plant		H2O2-induced osteoblast apoptosis in MC3T3 cells, Untargeted zebrafish metabolomics (UPLC-Q-Orbitrap-HRMS)	VPOP1 ↓ apoptosis in MC3T3 cells by modulating mitochondrial pathways (Bcl-2, caspase-3, Bax, cytochrome C); intervened in arachidonic acid, tyrosine, phenylalanine, and sphingolipid metabolism.	Antioxidant, Anti-osteoporotic, Apoptosis inhibition.	Maybe
20	El-Nawary et al. 51	POS (P.oleracea stem)-powder, POS-infusion, POS-ethanolic70%	Stems	POS-powder 10%, POS-infusion and POS-ethanolic 70% 1.0 g/kg	Dietary hyperlipidemic Wistar Albino rats (8-week experimental period)	↓ body weight gain, feed intake, total cholesterol, triglycerides, LDL-C, VLDL-C; ↑ HDL-C levels;	Hypolipidemic, hepatoprotective, weight-lowering	No
21	Alfwuaires et al.39	Ethanolic extract of Portulaca oleracea leaves	Leaf	200 mg/kg body weight for 7 days	Acetic acid (AA)-induced ulcerative colitis in mice	↓ body weight, colon length, and colon weight/length ratio; ↓ inflammatory mediators (IL-1, IL-6, IL-17, TNF-α, IFN-γ, NF-κB); ↓ MPO activity; ↓ fecal calprotectin; ↓ total bacterial concentration in the colon.	Immuno-modulatory, anti-inflammatory, colonic healing, gut microbiota modulation	Maybe
22	Catap et al.46	Ethyl acetate (EA) extract	Leaf	50 mg/kgBW EA	In vivo study using ICR mice	↑ phagocytosis, ↑ lymphocyte proliferation ↓ intestinal motility (comparable to atropine)	Immuno-modulatory and antispasmodic	No
23	Wang et al.28	Phenolic extract (PAAs) containing indoline amides	Whole plant	L-PAAs: 360 mg/kg/day H-PAAs: 720 mg/kg/day Piracetam (positive control): 400 mg/	Senescent Kunming mice with cognitive dysfunction induced by D-galactose (1250 mg/kg/day) and NaNO2 (90 mg/kg/day) for 8 weeks	L-PAAs & H-PAAs ↑ cognition, ↓ oxidative stress, ↑ SOD & CAT, ↓ MDA, ↓ hippocampal damage. H-PAAs > L-PAAs, similar to Piracetam.	Antioxidant, cognitive enhancer, anti-aging, and neuroprotective.	Maybe
24	Tao et al. 52	Polysaccharide (POP)	Whole plant	600 mg/kg/day	In vitro (PC12 cells) & in vivo (Pb-induced cognitive impairment in rats)	↓ ROS, ↑ PC12 cell viability ↑ cognition, ↓ escape latency, ↑ platform crossings (Morris water maze) ↑ dendritic spine density in CA1 & DG	Neuroprotection against Pb-induced cognitive impairment	No
25	Samir et al.29	Aqueous extract	Leaf	400	$AlCl_3$ (200 mg/kg/day)-	↓ MDA, WBC, lymphocytes,	Antioxidants &	Maybe

No	References	Extracts/ Components	Medicinal Parts	Doses	Study Model	Core mechanism/Result	Therapeutic effects category	Effects Related to AMS
				mg/kg/day	induced liver toxicity in Wistar rats	monocytes, platelets, GPT activity, total cholesterol ↑ GSH, GST, SOD levels	hepatoprotective	
26	Yehia et al.53	aqueous extract	Aerial part	injection 200 mg/kg every other day for 4 weeks	Genetically diverse Collaborative Cross (CC) mice (13 lines), fed either a high-fat diet (HFD, 60% fat) or control match diet (CMD, 10% fat)	HFD Group: ↓ Glucose levels (after 4-week PO treatment). ↑ Body weight during the dietary challenge. ↑ Glucose intolerance (IPGTT-AUC). Male mice responded more strongly to PO treatment than females. CMD Group: Females: ↓ Glucose levels after PO treatment. Males: No significant effect observed.	Antidiabetic	No
27	Seif et al.30	Ethanolic extract	Aerial part		Male rats treated with cadmium chloride to induce hepato-nephrotoxicity	↓ Elevated liver enzymes (restored to normal levels). ↓ Creatinine (restored to normal levels) ↓ Serum MDA levels. ↑ Activities of antioxidant enzymes	Hepato-nephroprotective and antioxidant	Maybe
28	Karimi et al.31	Purslane capsule	Aerial part	500 mg capsule 2x/day 12 weeks	Double-blinded randomized controlled clinical trial; 86 RA patients aged 20–79.	↓ Visual analog scale, swollen joint count, tender joint count, disease activity score (DAS28). ↑ SOD and TAC. ↓TNF-α and ESR. ↓ hs-CRP.	Anti-inflammatory, antioxidant, and rheumatoid arthritis reliever.	Maybe
29	Elharrif 41	Ethanolic Extract	Aerial part	High-dose: 300 mg/kg body weight Low-dose: 150 mg/kg body weight	Male albino rats with induced arthritis and obesity	Purslane extract (150 and 300 mg/kg) ↓ cholesterol, triglycerides, LDL-cholesterol, total cholesterol, CRP, ESR, RF, anti-CCP.	Anti-inflammatory, Lipid-lowering, Metabolic modulation	Maybe
30	Sahreni et al.44	Portulaca oleracea leaf extract	Leaf	60 mg/200g BW, 90 mg/200g BW, 110 mg/200g BW	Alloxan-induced diabetic rats	↓ Malondialdehyde (MDA) levels at 90 mg/200g BW dose	Antioxidant	Yes
31	Sahreni et	Portulaca	Leaf	61	Alloxan-induced	↓ blood sugar levels with 60 mg/200g	Antidiabetic	No

No	References	Extracts/ Components	Medicinal Parts	Doses	Study Model	Core mechanism/Result	Therapeutic effects category	Effects Related to AMS
	al.32	oleracea leaf extract		mg/200g BW, 90 mg/200g BW, 110 mg/200g BW	diabetic rats	BW the most effective dose		
32	Putra et al.47	Ethanol extract	Aerial part	100 mg/kg BW, 200 mg/kg BW, 400 mg/kg BW	Male rats (Rattus norvegicus)	↓ Foot volume change (immunomodulatory effect) at all doses (100 mg/kg BW, 200 mg/kg BW, 400 mg/kg BW)	Immuno-modulator	No
33	Azizah et al.42	Hot water infusion (Krokot tea)	Aerial part	7.5 g/L	Rats with rheumatoid arthritis	↓ TNF-α by 41.0% ↓ IL-1 by 58.9%	Anti-inflammatory, Immuno-modulator	Maybe
34	Salim et al.43	Ethanol Extract	Aerial part	100 mg/kgBW, 200 mg/kgBW, 400 mg/kgBW	Rats (Hind paw edema induced by carrageenan)	↓ Edema volume by 34.80% (100 mg/kgBW), 36.90% (200 mg/kgBW), and 40.04% (400 mg/kgBW)	Anti-inflammatory	Yes

4) Experimental & Observational studies related to *Portulaca oleracea* and AMS

Based on searches conducted in databases such as Google Scholar, PubMed, and ScienceDirect, covering a broader range of publication years, no study has specifically addressed the relationship between *Portulaca oleracea* and Acute Mountain Sickness. However, only one study by Yue *et al*. investigated *Portulaca oleracea* in rats to examine its therapeutic effects related to the severe form of Acute Mountain Sickness, which is High Altitude Pulmonary Edema (HAPE).[54] Additionally, two studies explored the antihypoxic effects of *Portulaca oleracea*, as hypoxia is one of key factor in the pathogenesis of Acute Mountain Sickness.[55,56]

The study by Yue *et al*.[54] demonstrated the protective effects of the ethanol extract of *Portulaca oleracea* (EEPO) against hypoxia-induced pulmonary edema. This condition is analogous to severe AMS symptoms like High Altitude Pulmonary Edema (HAPE). The study identified mechanisms such as reduced vascular leakage, decreased oxidative stress, and inhibition of proinflammatory cytokine expression. These findings align with the pathophysiological mechanisms of AMS, where hypoxia leads to endothelial dysfunction and inflammation. The observed dose-dependent efficacy of EEPO in reducing edema and oxidative stress underscores its therapeutic potential for altitude-related hypoxic conditions.[54]

While direct studies linking *Portulaca oleracea* to Acute Mountain Sickness (AMS) are limited, experimental investigations have explored its pharmacological effects in hypoxic conditions, which are pivotal to AMS pathophysiology. Chen *et al*. examined the anti-hypoxic activity of ethanol extract of *Portulaca oleracea* (EEPO). Their findings highlighted EEPO's capacity to enhance glycolytic enzyme activity and maintain ATP levels under oxygen-deprived conditions. By stabilizing metabolic processes during hypoxic stress, EEPO potentially alleviates tissue energy deficits—a critical factor in AMS, particularly in the brain and pulmonary cells, where hypoxia-induced damage is most severe.[55]

Moreover, the neuroprotective properties of EEPO have been substantiated by Wanyin *et al*. who reported its role in modulating endogenous erythropoietin (EPO) expression. This modulation, mediated through the stabilization of Hypoxia-Inducible Factor 1-alpha (HIF-1α), enhances cellular resilience against hypoxia-induced apoptosis and damage. Given that cerebral hypoxia contributes significantly to AMS pathogenesis, the ability of EEPO to upregulate EPO underscores its potential as a neuroprotective agent in managing AMS-related symptoms.[56]

Although no human clinical trials have directly connected *Portulaca oleracea* with AMS, these experimental findings align with the underlying mechanisms of AMS pathophysiology. EEPO's effects in reducing oxidative stress, preserving vascular integrity, and supporting metabolic and neuroprotective processes suggest its value as a therapeutic candidate for altitude-related conditions. These insights advocate for further research to explore the clinical relevance of *Portulaca oleracea*

CONCLUSION

This review highlights the potential of *Portulaca oleracea* as a natural remedy for mitigating the physiological challenges of high-altitude environments, particularly Acute Mountain Sickness (AMS). While direct human studies linking *P. oleracea* to AMS remain limited, its pharmacological properties, including antioxidant, anti-inflammatory, and antihypoxic effects, align with the pathophysiology of AMS. The presence of bioactive compounds such as flavonoids, alkaloids, and organic acids reinforces its potential therapeutic role. Experimental evidence, particularly from ethanol extract studies (EEPO), underscores its ability to modulate metabolic processes, reduce oxidative stress, and enhance resilience to hypoxic conditions. To deepen our understanding and maximize the potential of *P. oleracea* in AMS management, future studies employing in silico approaches like network pharmacology, molecular docking, and molecular dynamic simulations are recommended. These methods can elucidate the molecular interactions between *P. oleracea*'s bioactive compounds and key targets involved in AMS pathogenesis, such as hypoxia-inducible factors (HIFs), inflammatory cytokines, and oxidative stress pathways. Such computational

techniques can also identify synergistic effects and optimize compound formulations for clinical applications.

From a broader perspective, *P. oleracea* offers significant opportunities for the medical and wellness tourism sectors. As wellness tourism continues to expand, particularly in regions with high-altitude trekking and climbing destinations, the integration of natural remedies like *P. oleracea* into health-focused travel packages can enhance the overall experience for travelers. By promoting evidence-based natural therapies, destinations can position themselves as leaders in sustainable and holistic health tourism. Moreover, clinical validation of *P. oleracea* as a preventive or therapeutic agent for AMS could attract medical tourists seeking effective, natural solutions for altitude-related conditions. In conclusion, *P. oleracea* represents a promising candidate for AMS prevention and treatment. With further research, including computational and clinical studies, its potential can be fully realized, contributing not only to altitude medicine but also to the evolving landscape of medical and wellness tourism.

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