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Review

Medicinal plants in the space exploration era: challenges and perspectives

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Table S1. Milestones in the history of space travel. 32

Date	Event	Agency/Country
20 June 1944	Launch of the V-2 rocket, the first human-made artificial object to reach outer space by crossing the Karman line.	Germany
24 October 1946	First picture of the Earth taken from outer space by a camera installed in the V-2 No. 13 rocket.	U.S.A.
04 October 1957	Launch of the Sputnik-1, the first artificial satellite.	Soviet Space Program, URSS
03 November 1957	Launch of the Sputnik-2, the first satellite with a living animal on board (the dog Layka).	Soviet Space Program, URSS
12 September 1959	Launch of the Luna-2, the first spacecraft hard-landing the surface of a celestial body (Moon).	Soviet Space Program, URSS
12 April 1961	Launch of the Vostok-1, the first spacecraft with a human being on board. Jurij Alekseevič Gagarin was the first human to reach the outer space and orbit Earth.	Soviet Space Program, URSS
16 June 1963	Launch of the Vostok-6, the first spacecraft with a woman on board. Valentina Tereškova was the first woman to reach the outer space and orbit Earth.	Soviet Space Program, URSS
26 July 1963	Launch of Syncom-2, the first telecommunications satellite to operate in geosynchronous orbit.	NASA, U.S.A
15 July 1965	Mariner-4 was the first spacecraft to transmit the picture of the surface of another planet (Mars).	NASA, U.S.A
21 December 1968	Launch of the Apollo-8, the first crewed spacecraft to leave Earth's orbit, to reach and orbit Moon and to safely return to Earth. Frank Borman, James Lovell, and William Anders were the first humans to see the far side of the moon and to take a picture of Earthrise.	NASA, U.S.A
16 July 1969	Launch of the Apollo-8, the first crewed spacecraft to land on Moon's surface. Neil Armstrong and Buzz Aldrin were the first humans to step onto Moon' surface.	NASA, U.S.A
17 August 1970	Launch of the Venera-7, the first spacecraft to soft-land on another planet (Venere) and to transmit back data to Earth.	Soviet Space Program, URSS

Date	Event	Agency/Country
12 September 1970	Launch of the Luna-16, the first remote-controlled spacecraft to carry back lunar samples.	Soviet Space Program, URSS
19 April 1971	Launch of the Salyut-1, the first space station.	Soviet Space Program, URSS
28 May 1971	Launch of the Mars-3, the first spacecraft to soft-land the Mars's surface.	Soviet Space Program, URSS
30 May 1971	Launch of the Mariner-9, the first spacecraft to orbit Mars and to transmit images of its satellite (Phobos and Deimos).	NASA, U.S.A
06 **June 1**971	Launch of the Soyuz-11 with three cosmonauts on board: Georgij Timofeevič Dobrovol'skij Viktor Ivanovič Pacaev and Vladislav Nikolaevič Volkov. It represented the first crew to live and work in a space station (about 3 weeks). The cosmonauts tragically died for a technical problem while preparing the re-entry. To this day, they remain the only humans to have lost their lives in space.	Soviet Space Program, URSS
14 May 1973	Launch of the Skylab, the first and only space station exclusively operated by the United States.	NASA, U.S.A
20 August 1975	Launch of the Viking 1, the spacecraft that transmitted the first image of the Mars's surface.	NASA, U.S.A
12 April 1981	First flight of the Space Shuttle Program. The space shuttle Columbia was the first reusable spacecraft in the story of space travel. The Columbia, with two astronauts on board, returned to Earth two days later.	NASA, U.S.A
02 July 1985	Launch of the Giotto, the first spacecraft to fly-by a comet (Halley's comet).	ESA, Europe
19 February 1986	Launch of the core module of the modular space station Mir. Mir was the first continuously inhabited space station in orbit; it remained operational until 23 March 2001 when it was deorbited.	Soviet Space Program, URSS

Date	Event	Agency/Country
18 October 1989	Launch of the Galileo spacecraft. It was the first spacecraft to orbit Jupiter (it arrived at the planet on 7 December 1995) and to launch an atmospheric probe in its atmosphere.	NASA, U.S.A
17 February 1996	Launch of the Eros, the first spacecraft to orbit (14 February 2000) and soft-land (12 February 2001) on a near-Earth asteroid (Eros).	NASA, U.S.A
15 October 1997	Launch of the Cassini-Huygens, the first spacecraft to orbit Saturn (with the orbiter Cassini, 01 July 2004) and to soft-land on the surface's satellite of a planet other than Earth (Saturn's moon Titan, with the lander Huygens, 14 January 2005).	NASA (U.S.A), ESA (Europe), ASI (Italy)
20 November 1998	Launch of the first module of the International Space Station. The ISS is the largest space station ever built and is currently operational.	NASA (U.S.A.), Roscosmos (Russia), ESA (Europe), JAXA (Japan), and CSA (Canada)
9 May 2003	Launch of the Hayabusa, the first spacecraft to return to Earth, seven years later, with soil samples from an asteroid (the asteroid 25143 Itokawa).	JAXA, Japan
2 March 2004	Launch of the Rosetta-Philae (orbiter-lander), the first spacecraft to orbit a comet (6 August 2014, comet 67P/Churyumov–Gerasimenko) and to land in its surface (12 November 2014).	ESA, Europe
11 May 2004	Launch of the Messenger, the first spacecraft to orbit Mercury (18 March 2011)	NASA, U.S.A
21 June 2004	First sub-orbital flight of privately funded spacecraft (SpaceShipOne). The pilot of the flight was Mike Melvill.	Scale Composites, U.S.A.
19 January 2006	Launch of the New Horizons, the first spacecraft to fly-by Pluto and Charon (14 July 2015), the largest of its satellites. On first January 2019, the New Horizons fly-bys 486958 Arrokoth, the farthest object in the solar system explored by a spacecraft.	NASA, U.S.A

Date	Event	Agency/Country
27 September 2007	Launch of the Dawn, the first spacecraft to orbit a dwarf planet (Ceres, 6 Match 2015)	NASA, U.S.A
21 December 2015	First vertical landing of an orbital-class rocket booster. It allows the booster to be reused reducing launches' cost.	SpaceX, U.S.A.
03 January 2019	First landing of a spacecraft on the far side of the Moon.	CMSA, China
10 February 2020	Launch of SolO, the first solar orbiter developed to provide close-up views of the Sun, including its poles, and to study the solar activity.	ESA (Europe), NASA (United States),
30 May 2020	SpaceX Demo-2, the first private crewed test flight to the ISS aboard the Crew Dragon spacecraft.	SpaceX, U.S.A.
29 April 2021	Launch of the first module of the Tiangong, a space station constructed by China. It is currently operational.	CMSA, China
16 September 2021	Inspiration-4, the first orbital spaceflight with only private citizens aboard.	SpaceX, U.S.A.
8 April 2022	Axiom Mission 1, the first all-private astronaut mission to the ISS	Axiom Space (U.S.A.), SpaceX (U.S.A.)
23 March 2023	Launch of Terran 1, the first two-stage small-lift launch vehicle almost completely 3D-printed.	Relativity Space, U.S.A
23 August 2023	Soft landing of Chandrayaan-3 (with the lander Vikram). India became the fourth country to do a soft lunar landing, and the first to reach the lunar south polar region.	ISRO, India
03 May 2024	Launch of Chang'e-6, first robotic mission to retrieve samples from the far side of the Moon (25 June 2024).	CMSA, China

4.1. Therapeutic Potential of Phytochemicals in Space Medicine 38

4.1.1 Use of medicinal plants as alternative medication for sleep disorders 39

***Valeriana officinalis* L.**, commonly known as valerian, is a perennial herb belonging to the Caprifoliaceae family and represents the most studied medicinal plants for managing sleep disorders [1]. Besides the hypnotic effect, the root extract of valerian exhibits antioxidant, antimicrobial, anti-inflammatory, sedative, anxiolytic, spasmolytic, anticonvulsant, cytoprotective, and neuroprotective activities [2]. Valerian root extract (VE) has a complex composition [3], but its hypnotic action appears to be attributable to valerenic acid, a bicyclic sesquiterpenoid. Valerenic acid enhances GABAergic neurotransmission directly by acting as a positive allosteric modulator of specific GABA-A receptor subpopulations [4], and indirectly by inhibiting the catabolism of gamma-aminobutyric acid (GABA) [5]. Numerous clinical studies have been conducted over time to demonstrate the efficacy of VE in improving sleep disorders. These studies have yielded conflicting results, likely due to differences in the extract, dosage, timing of administration, and inclusion criteria for the trial subjects [6,7]. However, a recent review of randomised controlled trials, conducted in patients with a diagnosis of insomnia, revealed an overall improvement of symptoms following administration of VE [1]. In comparative clinical studies, the efficacy for VE was comparable to that of the benzodiazepine oxazepam [8,9]. Interestingly, the hypnotic effects of VE have been also observed testing poli-herbal preparation containing hop [10,11] or hop and passiflora [12]. In all clinical studies VE was found to be safe and well tolerated. 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56

***Croccus sativus* L.** is a medicinal herb belonging to the Iridaceae family that has been widely studied for its promising beneficial effects on neurological and neuropsychiatric disorders [13]. The pharmacologically active part of the plant is represented by the stigmas of the flower which, once dried, take the name of saffron [13]. Saffron is reach of pharmacologically active ingredients, and among them the most relevant are crocin, safranal and picrocrocin [14]. Saffron has antioxidant and anti-inflammatory activity [15], and evidence exists showing its ability to modulate serotonin, dopamine, norepinephrine and glutamate neurotransmission [16]. Based on these pharmacological effects, saffron has been studied as potential treatment for anxiety, depression, epilepsy and neurodegenerative diseases [13]. Furthermore, several meta-analyses of available clinical studies have highlighted the ability of saffron treatment to improve insomnia symptoms without causing significant adverse events [17–19]. Evidence exists suggesting that this effect may be mediated by the interaction of safranal with the benzodiazepine site in the GABA-A receptor [20]. 57 58 59 60 61 62 63 64 65 66 67 68

***Lavandula angustifolia* Mill.** (synonym of *Lavandula officinalis* Chaix), commonly known as lavender, is an evergreen shrub belonging to the Lamiaceae family. Lavender essential oil (LavEO) is recognized for its potential therapeutic activity, mainly including relief from pain, stress, anxiety, and insomnia [21]. The essential oil contains about 100 compounds, and among them, the monoterpenes linalool (25%-46%) and linalyl acetate (20%-45%) are the most abundant [22]. In most clinical studies, the predominant route of administration of LavEO is inhalation, and the treatment is therefore called aromatherapy [21]. Therapies based on the inhalation of aromatic essences of plant origin are enjoying increasing success, not only for the treatment of sleep disorders but more generally for promoting general well-being [23,24]. The rationale behind the effectiveness of aromatherapy is based on the hypothesis that inhaling aromatic oils positively modulates human emotions and physiological functions through the activation of limbic structures following stimulation of the olfactory system [23,24]. Furthermore, specific components in essential oils can modulate specific neurotransmission, inflammatory, or endocrine pathways [25]. Recent studies have revealed that inhaling LavEO improves several aspects of sleep disorders, while also reducing stress, anxiety and depression [26–29]. In addition to its effectiveness in aromatherapy, LavEO retains its hypnotic activity even when taken orally. Specifically, Silexan, a patented standardized LavEO for oral use, 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84

ameliorated insomnia because of its anxiolytic effect in patients suffering from anxiety disorders [30–33]. The exact mechanism underlying the hypnotic activity of LavEO has not been fully elucidated. Lavender is known to exert a general depression on neural activity independently of its interaction with the GABA-A receptor (where, in fact, it acts as a receptor antagonist) [34]. Furthermore, lavender-induced sleep improvement in anxious patients appears to be based on its potentiation of serotonin 5-HT1A receptors [35] and concomitant inhibition of voltage-gated calcium channels [36].

***Melissa officinalis* L.**, commonly known as lemon balm, is a perennial herbaceous plant belonging to Lamiaceae family. Folk medicine claims the use of lemon balm as calming agent and to ameliorate digestive tract disturbance [37]. Several studies confirm the potential therapeutic value of lemon balm demonstrating its antioxidant and anti-inflammatory properties [38]. Furthermore, lemon balm extract has been found to elicit positive effects on the central nervous system; it has beneficial effects on anxiety and depression, improves cognitive performance and has neuroprotective activity [37]. Phytochemical studies revealed that lemon balm extract is rich in pharmacological active ingredients such as volatile compounds, triterpenes, phenolic acids, and flavonoids [39]. Clinical trials investigating the ability of lemon balm to manage sleep disturbances have produced promising but conflicting results, with some of them showing an improvement of sleep quality and quantity [40–44] while other investigation failed to detect significant effects [45,46]. The poor bioavailability of some active compounds in lemon balm may be the cause of this lack of reproducibility. This is confirmed by a recent clinical study in which insomnia was successfully treated using a phytosomal formulation of standardized lemon balm extract, which aimed to increase the bioavailability of the active polyphenolic components [47]. The beneficial effects of lemon balm on sleep appear to be mediated, at least in part, by rosmarinic acid through direct stimulation of GABA-A receptors [48] and indirect enhancement of GABAergic transmission secondary to inhibition of GABA transaminase [49].

4.1.2 Use of medicinal plants as alternative medication for pain

***Capsicum annum* L.** (Ca) is an herbaceous plant belonging to Solanaceae family. There are several species of the Capsicum genus whose domestication dates back approximately 6,000 years, but Ca is the most widely cultivated and economically important for both culinary and medicinal uses. Available preclinical in vitro and in vivo studies attribute numerous pharmacological activities to Ca fruits or its components, such as antioxidant, anti-inflammatory, antifungal, antimicrobial, gastroprotective, antihyperlipidemic and immunomodulatory activities, which may explain its uses in traditional medicine [50]. The broad pharmacological spectrum of Ca reflects its complex phytochemical composition including several classes of bioactive compounds: carotenoids, phenolic acids, flavonoids, saponins, capsaicinoids, vitamins (C, E, and A), and volatile molecules [50]. Among them capsaicin is the most important pharmacologically active compound. For pain management Ca or capsaicin has been commonly applied topically in the form of patches, gels or creams. Several clinical studies have highlighted the ability of Ca plasters to effectively relieve various forms of pain such as low back pain [51–53] chronic soft tissue pain [53] and post-surgery pain [54]. The efficacy of Ca plasters was also confirmed by studies showing that Ca plaster use can reduce postoperative analgesics requirement [55,56]. These promising results have been confirmed and extended by clinical studies investigating the analgesic activity of topical applications of capsaicin in patients suffering from acute and chronic pain [57–59]. Ca and capsaicin topical application was reported as being safe and well-tolerated, with no systemic toxicity. The most reported side effects, including erythema, pain, itching, burning, and edema, are limited to the application site and depend on the concentration of capsaicin [60]. The analgesic effect of capsaicin is mediated by the transient receptor potential cation channel subfamily V member 1 receptor (TRPV1r). Prolonged exposure to capsaicin activates TRPV1r on nociceptors triggering a cascade of events including an initial algesia followed

by defunctionalization of TRPV1r and consequent ablation of nociceptive afferents resulting in sustained reduction of pain perception [61]. This process is reversible but has the therapeutic advantage that a single exposure to capsaicin for a short period of time (30-60 minutes) provides pain relief that can last weeks (up to three months in some clinical studies) [58,60].

***Curcuma longa* L.**, also known as turmeric, is a perennial, rhizomatous, herbaceous plant belonging to Zingiberaceae family. The root, a large cylindrical and branched rhizome, is the part of the plant of greatest interest both to produce spices and for its medicinal value. Turmeric has been used for centuries in various traditional medical systems, mainly in India, Egypt and China for wound healing and to alleviate gastrointestinal problems and inflammatory diseases [62]. The medical use that has been made of it in folk medicine is justified, at least in part, by studies showing that turmeric has antioxidant, anti-inflammatory, antimicrobial, anti-diabetic and hepatoprotective activity [62,63]. The main classes of bioactive compounds found in turmeric rhizome are essential oils (sesquiterpenoids, monoterpenoids and norsesquiterpenoids) and curcuminoids (curcumin, demethoxycurcumi, and bisdemethoxycurcumin) [64]. Curcumin, the main component of turmeric, has low water solubility and poor bioavailability which requires its use in high doses. Furthermore, several strategies have been developed to improve the bioavailability of curcumin, such as the inclusion of the turmeric extract in liposomes, polymeric micelles, microemulsions, and nanoparticles, or its combination with natural additives such as piperidine, genistein, and essential oils normally present in the turmeric rhizome [64]. Several recent clinical studies agree that turmeric treatment relieves joint pain and improves joint function in patients with knee osteoarthritis, regardless of the specific preparation used [65–67]. A synergistic analgesic effect was also noted combining turmeric extract with diclofenac suggesting its potential use in adjuvant therapies [68–71]. Interestingly, preliminary clinical studies suggest that turmeric extract, in combination with *Boswellia serrata* extract, could be a promising natural alternative also for low back pain [72,73] and musculoskeletal pain [74] relief. Overall, turmeric extracts were safe and well-tolerated with no evidence of severe adverse effects. Taken together, preclinical and clinical studies suggest that turmeric may mitigate pain specifically in conditions where inflammation and oxidative stress play a key role. Therefore, turmeric is believed to exert an analgesic activity by its antioxidant activity and by inhibiting several pro-inflammatory mediators and the production of inflammatory [69,75–77].

***Zingiber officinale* Roscoe**, commonly known as ginger, is an herbaceous perennial plant belonging to Zingiberaceae family. Like turmeric, ginger rhizome is consumed as a spice and used for its potential medicinal effects. Ginger is a common remedy used in traditional Eastern medical systems to treat cold, cough, nausea, gastrointestinal problems, pain, and arthritis [78–80]. The use of ginger in ethnomedicine is supported by a large body of preclinical evidence demonstrating that ginger extract has anti-inflammatory, antioxidant, gastroprotective and hepatoprotective activities, among others [81]. Bioactive compounds are abundant in ginger extract, mainly phenolic (gingerols, shogaols, paradols, zingerone) and terpene (zingiberene, α-curcumene, β-sesquiphellandrene) compounds [82]. Several meta-analyses have been conducted that have provided clear confirmation that ginger extract can relieve pain associated with osteoarthritis [83], dysmenorrhea [84], and migraine [85]. Furthermore, promising clinical data are emerging showing the potential analgesic activity of ginger extract in joint [86] and muscle [87] pain. Ginger extract was well tolerated, with mild and transient adverse effects reported (predominantly gastrointestinal). The analgesic effect of ginger extract results from the synergy of several mechanisms of action. The analgesic effect of ginger extract appears to result from the synergy of multiple mechanisms of action [88,89]: 1) the inhibition of the release of proinflammatory factors; 2) a free radical scavenging activity; 3) the activation of TRPV1 receptors; 4) the activation of specific subpopulations of serotonin receptors (5-HT_1, 5-HT_3 and 5-HT_5). Interestingly, ginger's ability to relieve pain by inhibiting the release of inflammatory markers has recently been confirmed in clinical settings [86].

Salix is a genus of plants, generally known as willow tree, belonging to Salicaceae family. The healing properties of willow trees have crossed time and space, having been known in virtually all cultures around the world [90]. The analgesic and anti-inflammatory properties of willow leaf extract were already known to the Sumerians and in ancient Egypt but was only in the 1824 that salicin (an alcoholic β-glucoside) was extracted from *Salix alba* bark and identify as its main bioactive component by Francesco Fontana and Bartolomeo Rigatelli [91,92]. Although research on salicin led to the synthesis of acetylsalicylic acid (Felix Hoffman, 1897), the therapeutic use of willow bark extract continues to arouse interest. Contrary to what one might expect, in fact, the mechanisms of action and adverse effects of aspirin and willow bark extract have little in common. In addition to salicin, willow bark extract contains other bioactive compounds (flavonoids, proanthocyanidins, and tannins) [93]; moreover, salicin is per se inactive and only a fraction of it is metabolized into biologically active salicylate derivatives [94]. Consequently, the analgesic and anti-inflammatory effects of willow bark result from the synergy of multiple mechanisms of action. Finally, willow bark extract has a better side-effects profile since, unlike aspirin, it does not damage the gastrointestinal mucosa and does not affect blood clotting [95]. Consistently, clinical studies have provided promising, though not conclusive, results in favor of the use of willow bark extract in the treatment of low back pain [96–98] and osteoarthritis [99].

***Harpagophytum procubens* (Burch.) DC. ex Meis** and ***Harpagophytum zeyheri* Decne.** (collectively composed of 5 subspecies), known as devil's claw, are perennial tuberous herbs belonging to the Pedaliaceae family that share the same pharmacological properties [100]. Devil's claw is native to Southern Africa, particularly the Kalahari Desert region, where its secondary tubers have been used for centuries in the local traditional medical systems. People used to prepare oral or topic formulations for the management of various types of pain (headache, toothache, heartburn, back-, menstrual-, muscular and joint pain), digestive disorders, fever and skin problems (burns, sores and boils) [101,102]. A growing body of preclinical in vitro and in vivo evidence has been gathered overtime to support the applications in folk medicine, demonstrating that devil's claw root extract or its main components have antioxidant, anti-inflammatory, analgesic, antimicrobial and anti-diabetic activity [101]. Phytochemical analysis revealed that devil's claw extract contains a variety of bioactive compounds responsible for its pharmacological effects, including iridoid glycosides (harpagoside, harpagide, procumbide, 8-O-p-Coumaroylharpagide), phenolic glycosides, flavonoids and triterpenes [102]. Clinical studies have further contributed to highlighting the promising analgesic activity of devil's claw extract specifically on low back pain [103] and osteoarthritis [104]. Devil's claw has also demonstrated an effectiveness level similar to that of authorized anti-inflammatory drugs [105–107]. There were no reports of serious adverse effects; the majority were gastrointestinal in nature and ranged from mild to moderate in severity. While the precise mechanism behind the analgesic effect of devil's claw extract remains unclear, its capacity to reduce oxidative stress and inhibit proinflammatory mediators and pathways likely contribute to its pain-modulating properties in inflammatory conditions [101]. Finally, a recent investigation underscored the involvement of the cannabinoid system in devil's claw activity, evidenced by enhanced CB2 receptor expression and suppression of endocannabinoid turnover [108].

***Boswellia serrata* Roxb** is a deciduous tree belonging to Burseraceae family, native to India, the Arabic peninsula, the horn of Africa and west Africa [109]. An oleo-gum resin known as Indian frankincense is derived from the bark of the tree and has been traditionally used in Ayurvedic and Unani medical systems to treat a range of ailments. Specifically, historical records describe the use of *B. serrata* resin (Bsr) in the management of inflammatory diseases and wound healing, with its psychoactive effects also noted in traditional use [110]. Modern scientific interest in its therapeutic potential began to intensify in the late 20th century, when researchers isolated boswellic acid (a pentacyclic triterpene) and its derivatives, which represent the main bioactive constituents responsible for its anti-inflammatory effects [111]. Clinical studies are now helping to confirm and

strengthen anecdotal and preclinical scientific evidence. Meta-analysis studies have in fact reported encouraging results specifically in the treatment of osteoarthritis [112,113], suggesting a favorable safety profile and therapeutic potential of Bsr in inflammatory-based diseases. *B. serrata* is also a valuable component in poly-herbal formulations with analgesic and anti-inflammatory activity [72–74,114]. As for the mechanism of action, the anti-inflammatory activity of *B. serrata* is expressed through the inhibition of 5-lipoxygenase (an enzyme crucial for the synthesis of leukotrienes) [111,115]. Moreover, *B. serrata* extract exhibits synergistic activity through additional mechanisms, including inhibition of human leukocyte elastase and reduction of oxidative stress [115,116]. Overall, unlike conventional nonsteroidal anti-inflammatory drugs (NSAIDs), Bsr reduce leukotriene synthesis while sparing prostaglandins and minimizing gastrointestinal toxicity.

4.1.3 Use of medicinal plants as alternative medication for space motion sickness (see main text)

4.1.4 Use of medicinal plants as alternative medication for skin diseases

***Aloe vera* (L.) Burm. f.**, belonging to the Asphodelaceae family, is a perennial succulent plant widely distributed in tropical and subtropical regions. Its use in traditional medicine dates back thousands of years for the treatment of burns, wounds, and various skin disorders [117]. The plant contains two major constituents with distinct chemical compositions: the gel obtained from the inner parenchymal tissue and the latex collected from the outer cortex [118]. A specific set of anthraquinones is responsible for the laxative, irritant, and allergenic effects of latex. Therefore, the manufacturing processes for aloe products focus on gel extraction, minimizing latex contamination. The gel extracted from the inner parenchyma of the leaves contains a complex mixture of polysaccharides (notably acemannan), anthraquinones, enzymes, vitamins, minerals and amino acids responsible for its pharmacological activity [118]. Preclinical studies have demonstrated *A. vera's* potent wound-healing, anti-inflammatory, and antimicrobial properties, mediated through enhanced fibroblast proliferation, collagen synthesis, and antioxidant activity [119,120]. Several clinical studies have confirmed that topical formulations containing *A. vera,* alone or in combination with other natural products, accelerate wound healing, reduce erythema, and relieve itching in patients with burns, psoriasis, or radiation-induced dermatitis [121,122]. Interestingly, oral administration of *A. vera* sterols has been demonstrated to improve skin hydration and elasticity, thereby promoting healthy skin [123,124]. Moreover, *A. vera* extracts have shown bacteriostatic activity against Staphylococcus aureus and Pseudomonas aeruginosa, supporting their role in infection control [125]. Topical *A. vera* preparations are generally safe and well tolerated, with rare cases of hypersensitivity or contact dermatitis reported. The beneficial effects of *A. vera* on skin are largely attributed to several mechanisms such as the ability to scavenge free radicals, to modulate inflammatory and immunomodulatory mediators and to promote re-epithelialization [120,126].

***Curcuma longa* L.** In addition to what is described above**,** turmeric exhibits a valuable activity in various dermatological disorders including acne, psoriasis, eczema, and photo-aging by virtue of its potent anti-inflammatory, antioxidant, antimicrobial, and wound-healing effects [127]. Clinical and experimental studies have shown that topical or oral curcumin formulations can reduce skin inflammation, enhance collagen deposition, and promote re-epithelialization in chronic wounds [128–130]. Turmeric is generally well tolerated, although contact dermatitis and mild irritation have been reported with concentrated topical preparations [131]. Its therapeutic benefits are primarily attributed to the modulation of oxidative and inflammatory pathways, particularly through inhibition of the NF-κB signaling cascade and activation of Nrf2 antioxidant responses [132,133].

***Calendula officinalis* L.** (Asteraceae), commonly known as marigold, is an annual herb native to the Mediterranean region and widely used in traditional and modern phytotherapy for its skin-healing

properties [134]. The flowers contain triterpenoids, flavonoids, saponins, carotenoids, and essential oils, which contribute to its anti-inflammatory, antioxidant, antimicrobial, anti-fungal, anti-cancer and analgesic effects [135–137]. Calendula extracts have demonstrated strong wound-healing activity in both preclinical and clinical models, primarily through the stimulation of angiogenesis, granulation tissue formation, and collagen metabolism [134]. Topical *C. officinalis* ointments and gels have shown efficacy in accelerating wound closure and reducing erythema and swelling in patients with burns, ulcers, and post-radiation dermatitis [138,139]. Mechanistically, Calendula's activity is attributed to the inhibition of cyclooxygenase and lipoxygenase pathways, coupled with increased antioxidant enzyme expression and collagen synthesis [140].

***Camellia sinensis* (L.) Kuntze**, the tea plant, is an evergreen shrub belonging to Theaceae family native to China and Southeast Asia. Tea has a thousand-year history as a beverage and is currently consumed by around 3 billion people worldwide, making it one of the most popular non-alcoholic drinks globally. In the traditional Chinese and Indian medical systems tea has been used for its stimulant, diuretic, and cardioprotective activities, as well as for wound healing [141]. Six main types of tea exist, defined by the processing method and the degree of oxidation of the leaves of *C. sinensis* plant: white, green, yellow, oolong, black, and dark (or post-fermented) tea [142]. Its leaves are rich in polyphenols—especially catechins such as epigallocatechin gallate (EGCG)—which possess strong antioxidant, anti-inflammatory, and photoprotective properties [143–145]. Purine alkaloids (mainly caffeine) are another relevant class of bioactive compounds found in *C. sinensis* leaves [144,145]. Numerous studies have reported that topical or oral administration of *C. sinensis* extracts can improve skin barrier function, prevent UV-induced oxidative damage, and alleviate symptoms of psoriasis, atopic dermatitis, and acne [146]. Clinical trials have shown that green tea–based creams reduce sebum production and lesion count in acne patients [147]. Moreover, EGCG has been shown to inhibit keratinocyte hyperproliferation and modulate inflammatory mediators such as IL-8 and TNF-α, which are key factors in psoriatic lesions [148]. Camellia sinensis formulations are generally safe and well tolerated, with no major adverse effects reported. Its protective and restorative effects on the skin are mainly due to its potent antioxidant capacity, suppression of proinflammatory cytokines, and regulation of skin immune responses [149,150].

***Hypericum perforatum* L.**, commonly known as St. John's wort, is a perennial herb belonging to the family Hypericaceae, native to Europe, North Africa, and Western Asia but now distributed worldwide [151]. It has been used for centuries in traditional medical systems for the treatment of wounds, burns, neuralgias, and mood disorders [152]. The aerial parts of H. perforatum contain a complex mixture of bioactive compounds, among which naphthodianthrones (hypericin), phloroglucinols (hyperforin), and various flavonoids (rutin, quercetin, hyperoside) are the most pharmacologically relevant [153,154]. These constituents exhibit antioxidant, anti-inflammatory, antimicrobial, anticancer and antidepressant properties that have been confirmed in numerous preclinical and clinical studies [153,155]. In addition, topical formulations of *H. perforatum* extract have been reported to improve symptoms of atopic dermatitis, mild plaque psoriasis, herpes virus and surgical or burn wounds, largely by modulating inflammatory mediators such as TNF-α and IL-6 and promoting keratinocyte differentiation, re-epithelialization, angiogenesis, wound contraction, and connective tissue regeneration [155–159]. The therapeutic effects of *H. perforatum* preparations on the skin are attributed to several mechanisms such as the ability to reduce oxidative stress, to modulate the expression of inflammatory mediators, and to promote keratinocyte differentiation, re-epithelialization, angiogenesis, wound contraction, and connective tissue regeneration [160]. When used topically, *H. perforatum* preparations are generally safe and well tolerated, though photosensitivity and mild irritation have been occasionally reported [160].

4.1.5 Potential use of adaptogens to increase resilience

***Panax ginseng* Meyer** is a perennial herbaceous plant belonging to Araliaceae family. The natural habitat of ginseng includes northeastern China, Korea, and the highland regions of eastern Russia. The root is the primary part used for medicinal purposes, and its classification into raw, white, or red ginseng depends on the method of processing [161]. The three forms differ for chemical composition, potency and uses. Widely regarded as one of the most well-known herbal remedies, ginseng has been valued for its therapeutic properties since ancient times, initially in Chinese and Korean traditional medicine. Its prominence gradually extended to the West and continues today [161]. In folk medicine, ginseng root extracts have been used to treat a multitude of medical conditions such as hypodynamia, anorexia, shortness of breath, palpitation, insomnia, impotence, hemorrhage, general weakness, inflammatory states and diabetes [162,163]. A wide range of preclinical studies have demonstrated the therapeutic potential of ginseng and its bioactive constituents, emphasizing their anti-inflammatory, antioxidant, immunomodulatory, anti-fatigue, cardioprotective, and neuroprotective effects [164]. Ginsenosides, a group of triterpene saponins, have been recognized through phytochemical studies as the principal active ingredients in ginseng root extract [165]. Other notable constituents include polysaccharides, peptides, alkaloids, polyacetylenes, and phenolic compounds [165]. Clinical research corroborates the adaptogenic properties of ginseng extract, with documented effects including decreased exhaustion [166–168], improved stress resilience [169,170], enhanced mental performance during demanding tasks [170–173], and elevated mood [170,173]. The mechanism behind ginseng's adaptogenic effect is intricate and involves multiple interconnected pathways, including the reduction of oxidative stress and pro-inflammatory factors, the modulation of inflammasome components, the regulation of the hypothalamic-pituitary-adrenal (HPA) axis, the modulation of monoamine neurotransmission and neurotrophic factors expression [164,174].

***Rhodiola rosea* L.** is a perennial herbaceous plant in the family Crassulaceae. Its natural distribution encompasses cold-climate and high-altitude regions of Europe, particularly Scandinavia, Siberia, and mountainous parts of Nord America and Asia. Traditionally, *R. rosea* root extract has been valued in Russian, Scandinavian, and Asian traditional medicine systems as a tonic to combat fatigue and sensation of weakness, improve physical performance, support mood, and help deal with stress and nervous system disorders [175–177]. Extensive preclinical studies have demonstrated that *R. rosea* and its constituents exhibit antioxidant, anti-inflammatory, cardioprotective, neuroprotective, anxiolytic, antidepressant and nootropic-like actions [176]. The observed pharmacological activities of *R. rosea* root extract are largely attributed to the presence of rosavins (phenylpropanoids) along with salidroside and tyrosol (both of which are phenylethanoid derivatives) [175,176]. Other classes of compounds present in *R. rosea* root extract are flavonoids, monoterpenes, triterpenes and phenolic acids [175,176]. In human clinical trials, *R. rosea* supplementation has been shown to reduce symptoms of physical and mental fatigue (especially under stress or demand) [178–180], enhance mental and physical performance [181,182], and improve mood disturbance [183–185]. The mechanisms behind the adaptogenic effects of *R. rosea* appear to be multifactorial, involving the modulation of the hypothalamic–pituitary–adrenal (HPA) axis (normalizing cortisol levels), the increase of monoamine levels in the brain (by blocking the enzyme monoamine oxidase), the stimulation of the expression and release of neuropeptide-Y and β-endorphins, the scavenging of reactive oxygen species, the upregulation of proteins protecting cells by stress-induced damages (e.g. heat shock proteins), and modulation of signaling pathways associated with cell survival, inflammation and stress resistance [176,177].

***Withania somnifera* (L.) Dunal**, commonly known as ashwagandha, winter cherry or indian ginseng, is a perennial shrub belonging to the Solanaceae family. Native to the arid landscapes of India, the Middle East, and sections of Africa, it has since been cultivated globally owing to its

recognized healing potential [186]. The roots are the most used part for medicinal purposes, though leaves, berries, and seeds also possess bioactive compounds. Since ancient times, ashwagandha has held a prominent place in Ayurvedic medicine, where it is regarded as a Rasayana—a herbal remedy believed to enhance longevity, vitality, and resistance to stress. [187]. Its therapeutic applications in traditional medicine, alone or as ingredient in poly-herbal formulations, include treatment for fatigue, neurological disorders, infertility, inflammation, pain and general debility among the others [188]. A growing body of preclinical studies supports the pharmacological efficacy of ashwagandha, highlighting its anti-inflammatory, antioxidant, anxiolytic, immunomodulatory, neuroprotective, antitumoral and anti-fatigue properties [186,189,190]. Withanolides—steroidal lactones structurally similar to ginsenosides—are considered the primary active constituents of *W. somnifera* extract [191]. Additional bioactive compounds include alkaloids, sitoindosides, flavonoids, and saponins [190–193]. Ashwagandha's adaptogenic efficacy is increasingly supported by clinical research, with reported benefits such as improved muscular strength and endurance [194–197], reduced stress-induced fatigue [198–200], better cognitive and executive functioning [201,202], lower perceived stress, and improved emotional well-being [203–205].

Mechanistically, ashwagandha extracts work in a complex and multi-target way to promote its adaptogenic effects, mainly through modulation of the hypothalamic-pituitary-adrenal (HPA) axis, attenuation of oxidative stress and neuroinflammation, and regulation of GABAergic neurotransmission [206].

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