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Medicinal plants from the Himalayan region for potential novel antimicrobial and anti-inflammatory skin treatments

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Abstract

Background and Objectives Adequate treatment of wounds remains one of the major medical needs globally, most notably in the regions with poor or limited access to health care. In many local and traditional systems of medicine, plants are often widely used for treating infected wounds.

Aim and objectives The overarching aim of this project was selection of potential species for use in a future treatment by combining with plant resources with aspects of antimicrobial photodynamic therapy (aPDT). Specifically, we focussed on species used locally in the Himalayan region for the treatment of skin disorders and then assessed the existing pharmacological evidence for key species based on the published evidence available.

Methods Database searches were performed to identify relevant publications describing local and traditional uses of plants in the Himalayan region of Bhutan, PR China, India, Nepal and Pakistan. Using the Global Biodiversity Information Facility (GBIF), species were researched in terms of their distribution including in different climatic regions, focussing on species mostly found in higher climatic zones (based on the Köppen–Geiger climate classification). For species used in three or more countries and restricted to the higher altitudes, data on safety, pharmacology, as it relates to dermatological conditions, and phytochemistry were retrieved.

Key findings The study identified a total of 606 species that are used in the treatment of various skin conditions often associated with infections reported in 84 articles. Common weeds like *Ageratum conyzoides* and *Bidens pilosa*, widely used and cultivated species like *Centealla asiatiaca* and *Prunus armenica* were excluded. This ultimately led to the identification of a core group of five widely used species restricted to the Himalayan region (*Cedrus deodara*, *Nardostachys jatamansi*, *Pinus wallichiana*, *Pinus roxburghii* and *Valeriana jatamansi*).

Conclusions Here we apply a novel approach comprising an assessment of the published information on the use of medicinal plants (i.e. local and traditional knowledge) in the context of their potential to be used in a biomedical form of clinical treatment – aPDT. Then, once sustainable sourcing based on access and benefit-sharing arrangements is in place, these species are investigated for their potential in wound treatment. Ultimately, the goal is to develop a new baseline for primary health care in some of the regions of the world with poor or limited access to health care.

Keywords: Himalaya; medicinal plants; wound treatment; traditional medicine; dermatology; infectious diseases (skin)

Introduction

Injuries account for 7.6% of deaths worldwide and 11% of years of life lost in 2019, especially in low- and low–middle-income countries.[1] Importantly, recovery of trauma patients may be severely disrupted by infections of wounds with microbes, leading to often long-term economic consequences due to temporary or permanent disabilities, considerable health costs and reduced or even ceased income.[2] This has a specific impact on the health-related quality of life and specifically the lives of the poor and poorest and their families, and all too often, women are more heavily affected, also in terms of access to health care.[3, 4]

Generally, a low bacterial load in open injuries is a critical goal in wound care to prevent delayed wound healing, difficult-to-treat chronic situations or – with certain pathogens – patients' death.[5, 6] However, especially in less- and medium-developed countries, as well as in poorer regions of other countries, established antibiotic treatment regimens are associated with a number of particular challenges. These include, among others, a limited drug availability for poorer segments of the population and, in rural areas, distribution of adulterated or poor-quality drugs, inappropriate prescription practices and unmonitored use of antimicrobials with risks of poor compliance and misapplication.[7] Especially the latter factors are known to contribute to the ever-growing development of antibiotic resistance, recognized as one of the most urgent challenges global public health care system currently facing.[8, 9]

Local and traditional medicinal plants are frequently recorded to be used in the prevention and treatment of infected wounds and for promoting wound healing. However, apart from the use in their natural state, some species identified from local pharmacopoeias have shown their potential to be a major source of new pharmaceutical leads like ingenol 3-angelate (used in dermatology) or galanthamine (with uses in cognitive decline).[10] Such leads are still largely underexplored but could serve to develop safe, cost-effective and efficient first-line treatments of wounds prone to infections, and, at the same time, prevent overuse of common antibiotics and eventually save last resort drugs.[11, 12]

In this basic research project, we wish to investigate natural molecules suitable for their potential application in innovative antimicrobial and wound-healing protocols. As a prerequisite for these studies, we here present a first literature search with the aim to identify plants that are generally used in the context of dermatological conditions. Such a search strategy broadens the spectrum of potential plant candidates because the vast majority of such diseases are associated with skin defects and/or a direct or indirect microbial involvement.

In essence, this can be seen as a classical approach, identifying potential lead species based on local/traditional uses.[13, 14] As this will normally lead to a large number of species and often very widely distributed ones, already studied in detail, we added a second step – the focus on plants particularly abundant in high mountain regions. As these plants are exposed to high levels of sunlight including UV, they are good candidates for plants rich in photoactive substances. Based on this botanical assessment, we then select species with potential therapeutic benefits.

For our research, we chose to further focus on plants from the Himalayan regions because they house many indigenous societies, who possess and apply knowledge of medicinal plants available to them. People in these regions often have poor access to biomedical ('Western') health care and treatments due to their remote location and poverty. These challenges combined with the fact that such regions are recognized as global biodiversity hotspots might have contributed to the maintenance of a thriving traditional medicine based on local medicinal species.[15–19] The exact number of Himalayan medicinal plants has not been reported, but the mountain range is a cradle for around 10 000 plant species.[19] The region spreads across five countries, namely Bhutan, China, India, Nepal and Pakistan, all of which retained a strong traditional medicine system, for example, the well-known and increasingly popular Ayurveda (India) and Traditional Chinese Medicine (TCM) (China). Bhutan sits on the Eastern Himalayas and features high mountains. Bhutan's official traditional medical system – *Sowa rigpa* – blends principles of Indian and Tibetan Medicine with ancestral medical applications.[20] Nepal is situated between the Western and Eastern Himalayas, featuring a unique blend of flora; over 6000 vascular plants in Nepal have been documented to date.[21] Due to the influence of neighbouring India and China, Nepalese traditional medicinal practices are now a combination of Ayurveda, Tibetan Medicine and local ethnomedicines.[21] Mixed climate zones, due to altitudinal variations (from 0 to 8611 m), endow Pakistan with a large diversity of plants (6000 flowering plants).[22] Similar to its neighbouring countries, Pakistan has a very rich experience of using plants to treat diverse ailments. However, in contrast to Bhutan and Nepal, the Pakistani traditional medicine system is based predominantly on Unani medicine.[23] Furthermore, the country has accepted Unani medicine and integrated it into the national health system, as well as other complementary and alternative medicine (CAM) systems, for example Ayurveda and homeopathy.[23]

A key aspect of our research on new herbal preparations for the treatment of infected wounds is the focus on herbal light-absorbing compounds. One of the best-investigated examples of such a natural photosensitizer molecule is hypericin, a hydroxylated phenanthroperylene dione occurring in flowers and leaves of *Hypericaceae* (the St John's Wort family).[24, 25] At least under *in vitro* conditions, light-activated hypericin has been shown to display a remarkable broad-band antimicrobial efficiency towards various bacteria, viruses, fungi and protozoa, including difficult-to-treat microbial biofilms and even antibiotic-resistant strains.[26, 27] While *Hypericum* extracts are well known to promote wound healing, their light-induced antimicrobial activity may significantly enhance this effect.[28] Several studies in patients already showed that wound disinfection by light-activated synthetic photosensitizers may impressively contribute to wound closure and healing.[29]

In view of our search for promising light-absorbing molecules, we thus furthermore systematically restricted the list of priority species to taxa being found in higher altitudes of the Himalayas.

Due to the shorter path length of the solar beam to the surface and thus lower amounts of absorbing and/or scattering atmosphere molecules, these regions are exposed to an intensive solar radiation.[30–32] Several studies indicated that enhanced light intensity and/or exposure to ultraviolet (UV) light is among the abiotic environmental stress factors eliciting an increased synthesis of secondary plant metabolites.[33–35] Many of these compounds may serve protective purposes, helping higher plants to cope with potentially harmful consequences of the strong irradiation, like oxidative damage resulting from increased levels of reactive oxygen species (ROS).[36] However, it had also been proposed that certain irradiation-induced secondary metabolites may serve as key survival and competitive factors in high mountain areas (with their environmentally harsh growth conditions and short vegetation periods) by contributing to an optimized phytochemical defense system against herbivores or pathogens.[37–40]

Not unexpectedly, the amount of UV absorbing molecules has been reported to increase with altitude.[41] However, in our context, it is important to note that this relation also applies to classical natural photosensitizers, as exemplarily shown with hypericin from *Hypericum perforatum* grown at higher mountain ranges in Turkey or Greece.[42, 43] In addition, studies indicated that at least under certain conditions, UV-B may increase the synthesis of hypericin.[44–46]

We here hypothesize that many more plants able to thrive or survive under prolonged strong solar irradiation (such as those found at high altitudes) have developed intensely light-absorbing molecules with a potential as clinical photosensitizers for photodynamic applications in patients. The endogenous roles of light-responsive compounds in altitude-adapted plants may be in preventing the impact of potentially damaging UV-induced ROS accumulation, but overall, the complexity of photoprotection in plants is not understood well.

The photophysical behaviour of hypericin and its analogues serve as an example that the effects in plants and animals or humans cannot be correlated, since it is clear that the compounds' pharmacological effects change dramatically with their biochemical environment, for example in the presence of proteins like human serum albumin.[47] This may lead to fundamentally different consequences of light-absorbing molecules in biological systems, as shown exemplarily with hypericism in grazing animals.[48]

Since clearly light-inducible effects pose the risks of secondary effects in humans, that is photoxicity, we have excluded species from this analysis, which are known to be highly phototoxic, that is cause major allergic reactions, act as pro-inflammatory agents or are damaging the skin directly.

To the best of our knowledge and based on an assessment of the literature, the combination of an ethnopharmacological with a phytogeographical approach presented here has never been attempted before and thus provides a novel strategy for the identification of potential natural photosensitizers for clinical photodynamic applications.

Methods

Literature search strategy

Literature was retrieved using three online bibliographical databases: Web of Science, Scopus, China National Knowledge Infrastructure (CNKI) and a detailed review of the 2015 edition of the Chinese Pharmacopoeia for species applied to treat skin diseases found in this region. The keywords originally used on Web of Science and Scopus were 'Bhutan', 'China', 'India', 'Nepal' or 'Pakistan' for the region, 'skin' or 'dermat*' for the disease of interest, 'Himalaya' or 'high altitude/elevation' to restrict habitat and 'plant'. As only a small number of articles were found, the search terminology indices were modified as follows: (a) Web of Science:[TOPIC: (Bhutan/China/India/Nepal/Pakistan) AND TOPIC: (skin/dermat*) AND TOPIC: (plant)]; (b) Scopus: TITLE-ABS-KEY (Bhutan/China/India/Nepal/Pakistan AND skin/dermat* AND plant). For CNKI, keywords – 'high altitude', 'plateau', 'Tibetan medicine', 'Himalaya', 'Changbai mountain' and 'Hengduan mountain' in Chinese were searched, restricted to 'Subject', and 'Synonym Search' was allowed. No time restrictions were included. The literature search is up to date until 10 August 2020. Plant names were assessed for taxonomic validity using *Medicinal Plant Names Services* (MPNS) *(mpns.science.kew.org*/mpns-portal). *The Plant List* (www.theplantlist.org), which was used in many published articles,[22, 49–52] was checked when MPNS provided confusing or no information about the plant name searched. The search result on MPNS was given priority when it contradicted that on *The Plant List*, or other specialist resources were consulted.

GBIF (www.gbif.org) was used to estimate the altitude range of species occurrences, with two datasets – The Himalayan Uplands Plant database and Database of Vascular Plants of Himalaya.

Inclusion and exclusion criteria

The inclusion criteria for literature were: (a) for CNKI, articles which were in the TCM category but also written in Chinese; (b) for Web of Science and Scopus, published articles in journals written in English; (c) papers reviewing plant species used to treat certain skin conditions of humans; (d) articles addressing a single herb's traditional uses; and (e) articles with the available full text. Papers were excluded if their study areas were far away from the Himalayas and provided no information about altitude.

Inclusion of a species was based on: (a) plant species with a clear description of traditional usage against skin ailment(s); (b) within the two datasets, plants with recorded occurrences at altitudes of at least 1000 m above sea level (asl).

Tabulation of plants

Titles and abstracts of search results were scrutinized, and a selection of full texts was made. A master list was developed with Microsoft Excel 2019 (Supplementary Appendix S1). The list includes the internationally accepted name, the name as published in the original source, family, habit, study region, plant part used, mode of preparation, route of administration, disease they were used for and the relevant sources. Species reported in more than one country were enlisted only once. Based on the information provided by *Flora of China*, CABI (https://www.cabi.org/isc/datasheet/55072*)*, Plants of the World Online (www.plantsoftheworldonline.org/*)*, GBIF (https://www.gbif.org/) and other biodiversity-related sources, four groups were created. These represent the general abundance of a species: '*' (generally restricted to montane areas above 1000 m), '#' (widely cultivated as a food, ornamental or for other purposes) or

'^' (widely distributed and generally weedy, or invasive). All others are listed with no symbol.

Review on pre-existing pharmacological evidence and phytochemistry of core species

Species used in three or more countries and restricted to the higher altitudes were reviewed for their safety and pharmacology as well as phytochemistry as it relates to dermatological conditions.

Literature search strategies for species selected were: (a) [TITLE-ABS-KEY (species name) AND TITLE-ABS-KEY (skin OR dermat*)] on Scopus; (b) TOPIC: (species name) AND TOPIC: (skin OR dermat*) on Web of Science. Species included in the TCM system were also searched on CNKI, (Subject: species name) AND (Title, Keyword and Abstract: uses recoded in Supplementary Appendix S1).

The literature inclusion criteria were: (a) for CNKI, papers written in Chinese; (b) for Web of Science and Scopus, published articles in journals written in English; (c) studies researching phytochemistry and/or pharmacology related to the positive effect on skin conditions of species searched; (d) articles reporting side effects caused by the administration of the plant's extracts; and (e) articles with the available full text. Additionally, the reference list of each paper was checked for relevant articles. Studies on polyherbal preparations were excluded. We followed Heinrich *et al*.[53] for assessing the quality of the studies under review.

Results and Discussion

Species used in high-altitude regions

In total, 84 articles, including 12 which focussed on a certain species or genus, were selected from the title and abstract according to the inclusion and exclusion criteria. Including the Chinese Pharmacopoeia, 85 publications in total were reviewed. Studies were distributed unevenly among the countries included. Most publications (34; 40%) targeted the local and traditional uses in Indian communities, followed by Pakistan (16; 19%), while China and Nepal had similar proportions (13; 15% and 14; 16%, respectively). By contrast, only four papers (5%) recorded botanical treatments in Bhutan, and from more than one country, respectively.

A total of 606 species representing 126 families are recorded as being used by indigenous people for cutaneous complaints, with Asteraceae (58 species), Fabaceae (42), Lamiaceae (32), Polygonaceae and Rosaceae (21, respectively) and Ranunculaceae (19) being the most commonly cited families (Supplementary Appendix S1). As one would expect, the majority of the included species are herbs (373, 61.5%), followed by shrubs (113; 18.6%) and trees (89; 14.7%). Very few climbers (25; 4.1%) and ferns (3; 0.5%) are recorded.

The number of medicinal species recorded in each country also varies greatly and is correlated with the number of papers, which to some degree also indicates varying degrees of research interest in these countries: India (340 species), Pakistan (190) and Nepal (156). Only 72 species from China 36 from Bhutan are included (multiple listings possible).

None of the species documented was used in all countries with five species recorded in four out of five countries for similar or different dermatological complaints: *Centella asiatica* (L.) Urb., *Melia azedarach* L., *Oxalis corniculata* L., *Ricinus communis* L. and *Zanthoxylum armatum* DC. *Ricinus communis* stands out as being particularly widely used (15 studies with records in 15 different categories of skin problems). Of note, all these species are widely distributed and, in many cases, weedy species, which are not endemic to high-altitude regions.

Local and traditional medical uses in the context of dermatological conditions

The terminology for dermatological conditions used in the papers was inconsistent. Similar diseases were recorded with different terms, such as chilblain and frostbite, tinea pedis and athlete's foot and leukoderma and leucoderma. Besides, catch-all terms like 'skin diseases' and 'dermatological disorders' were used to indicate ethnomedicinal applications. Also, a separated/attached form of terms for the same types of disorder (e.g. smallpox and small pox) occurred in different papers. Therefore, the data summarized in Table 1 represents a synthesis and cannot be correlated with standard biomedical terms (e.g. ICD11).

Wounds, cuts (which could be classed as a subcategory of wounds) as well as boils, stand out as being of particular importance. Wounds, boils and cuts were also the most common skin ailments in several studies investigating traditional dermatology practices in India and Pakistan.[11, 12, 22, 54–56] Specific reference to inflammatory and infectious conditions is relatively low, and in case of sunburns only two uses were recorded, for *Ephedra gerardiana* and *Sesamum indicum*. In addition, chilblains/frostbites are rarely treated. These data provide some indication of what particular health problems are treated in these high-altitude regions. For example, based on the data retrieved, chilblains/frostbite seems to be rarely treated or there is an underreporting of such uses. The reasons for this low number of reported species remain unclear.

Clearly, the uses for a single species may also differ widely. For instance, *A. conyzoides* L. is applied to wounds in Bhutan, India and Nepal, but it also plays a role in the treatment of leprosy and boils in India (Supplementary Appendix S1).

Achyranthes bidentata Blume is used to treat pimples, boils, itchy pustules and insect and snake bites in India, whereas in Chinese medicine it is mainly used for musculoskeletal conditions and was originally cited in texts of the 2nd century CE.[57] However, it could potentially have an application in skin diseases due to its steroidal content and its potential application in tissue regeneration.[58]

The top 12 species recorded for medicinal use in high-altitude regions are *Cedrus deodara* (Roxb. ex D.Don) G. Don, *Houttuynia cordata* Thunb., *Lobelia chinensis* Lour., *Nardostachys jatamansi (D.Don) DC*, *Paris polyphylla* Sm., *Pinus wallichiana* A. B. Jacks and *Pinus roxburghii* Sarg., *Prinsepia utilis* Royle, *Punica granatum* L., *Solanum nigrum* L., *Tussilago farfara* L. and *Valeriana jatamansi* Jones ex Roxb. Interestingly, seven of them are not typical of high-altitude regions – *H. cordata*, *L. chinensis*, *P. polyphylla*, *P. utilis*, *P. granatum* L., *S. nigrum* L., *T. farfara* L.

High-altitude medicinal species

An initial impetus for this review was the search for species, which – due to their exposure to high intensities of light – might be of particular interest for further research and development focussing on light-activated potential anti-infective and anti-inflammatory agents for treating wounds. We used a systematic strategy as outlined in Figure 1 to select the most promising species. Basing the selection criteria on the updated Köppen climate classification,[59] we took a very broad approach and included species which are restricted to or have their biodiversity centre in climate region Cwb and above (E – tundra and high mountains). However, we also included species

Table 1 Disease categories and number of species reported from Bhutan, China, India, Nepal and Pakistan

Disease category	Number of species recorded					
	Total	Bhutan	China	India	Nepal	Pakistan
Abscess	32	6	2	17	–	8
Acne	6	–	1	3	–	2
Animal bites (stings)	65	–	11	31	14	18
Blister	7	–	–	4	3	–
Boils	149	1	12	100	26	30
Burn (scald)	84	1	8	37	25	17
Carbuncle	38	–	27	8	–	3
Chickenpox	7	1	1	4	–	1
Chilblain (frostbite)	3	–	–	3	–	–
Corns	2	–	1	–	–	1
Crack (chapped hands and feet)	11	–	1	6	4	1
Cut	127	4	–	88	47	6
Dandruff	16	–	–	7	5	8
Dermatitis	10	–	3	1	–	6
Eczema	57	1	18	30	1	9
Erysipelas	5	–	4	1	–	–
Herpes	1	–	–	1	–	–
Inflammation	13	–	–	5	2	6
Itch (itching)	46	1	2	31	5	8
Leprosy	45	4	1	26	9	12
Leucoderma (leukoderma)	22	–	–	18	2	4
Measles	10	–	1	4	–	5
Pimples	52	–	–	23	8	24
Pus	2	–	–	1	1	–
Pustule	5	–	1	1	–	3
Rashes	4	–	–	1	1	2
Ringworm	41	–	1	27	8	7
Scabies	52	2	4	25	13	16
Skin allergy	16	–	–	11	1	4
Skin eruption	9	–	–	4	1	6
Skin/dermatological infections	52	2	4	15	2	29
Skin irritation	8	–	–	3	1	4
Skin/dermatological diseases/problems/disorders/complaints/ailments	174	6	2	84	37	56
Skin spots	3	–	–	1	–	2
Smallpox	9	–	1	6	–	2
Sores	51	1	35	8	5	3
Sunburn	2	–	–	–	1	1
Swelling	12	–	–	5	1	6
Thorn	1	–	–	1	–	–
Tinea pedis (athlete's foot)	4	–	2	1	–	1
Ulcer	15	–	5	3	1	6
Urticaria	4	–	3	1	–	–
Warts	12	–	1	2	–	9
Wound (skin damage, scar)	270	23	15	140	76	71

Most species are reported to be used in more than one disease category (Supplementary Appendix S1).

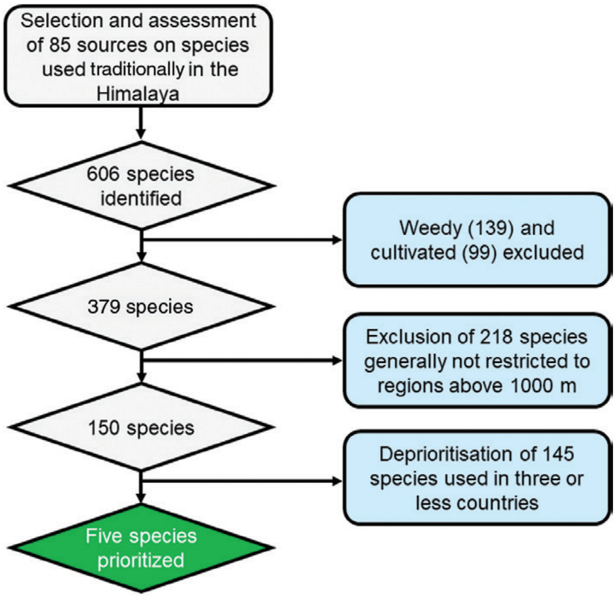

Figure 1 Flow diagram of species prioritization based on the combination of local/traditional uses for skin infections/inflammation and the use in high-altitude regions.

found in Cwa taking the reported altitude range for a species as an approximation.

Only five species restricted to the Himalayan region (*C. deodara*, *N. jatamansi*, *P. wallichiana/P. roxburghii* and *V. jatamans*) have been more widely used in the region. Species numbers used in only one, two and three countries are 125, 19 and 5, respectively. Among the 606 species, those generally restricted to or at least widely distributed in mountain regions account for less than a quarter (150 sp.) (Supplementary Appendix S1). This group includes Himalayan endemic species, as well as species with a distribution centre around the Arctic circle and in high mountain regions. Another core group is composed by commonly cultivated species (139; 23%), which are grown for ornamental purposes or for food, like the pomegranate (*P. granatum*) and maize (*Zea mays*). 99 species (16%) are widely distributed, weedy or invasive species. The remaining ones are species distributed both in higher and lower elevations of Asia.

These data are interesting from another perspective. It has been demonstrated before that the access to a resource to be used medicinally or in other words its 'weediness' is a core factor determining the selection of a plant, both in local/traditional medical systems, but also in biomedicine.[60, 61]

Plant parts used, preparation methods and modes of administration

The uses of plant parts for medicinal preparations were highly diverse, covering almost all parts but also different developmental stages (e.g. buds and flowers or leaves) (Table 2). Uses of the same parts of a species for different ailments and different parts for the same conditions were often documented (Supplementary Appendix S1). Leaves were the most frequently used part, followed by roots, whole plants, seeds and bark (similarly to other studies from India and Pakistan[12, 22, 54, 55]). The employment of leaves is preferable since it potentially offers a more sustainable use of natural resources, and since, compared to fruits and flowers, leaves satisfy medicinal demand for a longer period over an annual cycle.

In a dermatological context, the mode of preparation and formulation is of particular importance. However, this type of data is often lacking in ethnobotanical studies, such as those reviewed here (Supplementary Appendix S1).

Table 2 Plant parts used (based on Supplementary Appendix S1)

Part of plant used	Number of species (n = 1009[1])
Leaf	289
Root	148
Whole plant	123
Seed (kernel)	65
Bark	64
Fruit	59
Flower (floret, floral part, inflorescence)	57
Aerial part	37
Stem	25
Rhizome	24
Latex (milky sap)	19
Bulb	15
Tuber	10
Pseudobulb	10
Stem bark	9
Shoot	8
Root bark	6
Resin (oleoresin)	6
Branch	5
Peel (rind)	5
Berry	4
Bud, corm, gum	2 each
Bine, clove, corolla, dust, frond, endosperm, gall, petioles, pulp, spike, spore, stem node, twig, underground part, young saplings[1]	1 each

[1]A species may yield more than one drug.

The majority is made into pastes, followed by juice, decoction and powder (Table 3), in line with data from previous studies.[22, 54] Multiple uses of drugs from a species and modes of preparation are recorded in the studies reviewed, for example, the paste of *Trigonella foenum-graecum* L.: leaf (decoction, paste/oral), flowers (decoction, paste/oral), seed (paste/oral) (Supplementary Appendix S1). The decoction of *Celosia argentea* L. stems, leaves, flowers and seeds, respectively, was used as medicinal baths to treat eczema (Supplementary Appendix S1; Li *et al* 2006).

Clearly, in most cases, the formulations point to a potential use of the entire spectrum of metabolites (i.e. from hydrophilic to lipophilic) since the directly processed plant material is most commonly used (paste, juice, powder). Hydrophilic preparations (decoctions, poultice and infusion) are recorded in 114 (14.2%) cases; lipophilic preparations account for 5% (40) and in case of 'paste' the excipients remains unclear and often more detailed information on traditional preparation methods would have been essential.

As expected, a large majority of species with clear records of administration routes were used externally (359; 83%). Internal uses account for 16% (72), including species with both external and internal uses (including plant preparations from a botanical drug being used externally in one study and internally in another) (Supplementary Appendix S1).

The potential of high-altitude plants in the management of skin diseases

Several species retrieved from the literature search are widely used, and often they are common weeds or invasive species, which, in general terms, are already very well-studied. These include

Table 3 Frequency of use (number of species) for different preparation methods in the regions studied (based on Supplementary Appendix S1)

Preparation	Number of species (n = 801)[1]
Paste	259
Juice	120
Decoction	89
Powder	77
Extract	51
Poultice	50
Oil	40
Infusion	25
Raw material	22
Crushing	21
Fresh material	10
Heating	7
Cooking (frying)	6
Grinding, rubbing	5
Ash, pounding	4
Boiling	3
Crude, mashing, smoke	2 each
Cake, pill, warming	1 each

[1]Multiple drugs/forms of preparation possible.

A. conyzoides, *Bidens pilosa*, *C. asiatica*, *Cissampelos pareira*, *Euphorbia hirta*, *M. azedarach*, *O. corniculata*, *R. communis*, *Rubus ellipticus* and *R.* spp., *Urtica dioica*. *Cannabis sativa*, *P. polyphylla*, *Prunus armeniaca*, *Sapindus mukorossi*, *Vitex negundo* and *Woodfordia fruticosa*. Some like *P. armeniaca* are used relatively widely both for their fruit and as medicines, Others are well-studied medicinal plants and all these were excluded. The cases that will be examined are therefore those of the species more typical of high altitudes habitats and not widely used/known.

Cedrus deodara (Roxb. ex D.Don) G.Don

The essential oil of *C. deodara* is the main preparation reported with dermatological uses in India, Nepal and Pakistan (Supplementary Appendix S1). Controlling sarcoptic mange in sheep, was achieved using the essential oil of *C. deodara*.[62, 63]

Antifungal,[64] linked to two sesquiterpenes and anti-inflammatory/analgesic effects were also reported, and it is likely that the essential oil has antibacterial effects.[65]

Nardostachys jatamansi (D.Don) DC.

The species is found from Western to Eastern Himalaya including, Nepal, Tibet, as well as in other regions of North- and South-Central China, Bangladesh and Myanmar. In the Himalayas, some communities use the leaves to treat altitude sickness as well as wounds.[66] In Chinese medicine, its main use is in the treatment of digestive complaints.[57] While the traditional use of the root in three countries to treat wounds or fungal infections is well-known, limited information on relevant pharmacological effects is available. Ali *et al*.[67] demonstrate potential effects on benzoyl peroxide-induced oxidative stress, toxicity and ear oedema in mice and Min and Park[68] demonstrated inhibitory effects on inflammatory cytokines (IgE, IL-6, IL-8 and TNF-α) also in mice.

Bhattacharya and Dhiman[69] highlight the confusion between this species and *V. jatamansi* (see below). Since 1997 it has been listed by its synonym *Nardostachys grandiflora* in CITES Appendix II, as a plant of being at risk of becoming endangered unless trade becomes more sustainable.[70] It, additionally, figures in the IUCN Red List of Endangered Species.[69, 71]

Pinus wallichiana A.B. Jacks.

Pinus wallichiana is a mountain plant that provides a wide range of botanical drugs including stems, resin, leaves, bark and seeds that have been used in the traditional medicine of India, Nepal and Pakistan to treat cracks, cuts and wounds, pus and abscesses. Antibacterial, antifungal and anti-inflammatory activity have been reported, but the evidence remains limited.

Hydro-alcoholic extract of *P. wallichiana* stem bark showed a potent antimicrobial effect on *Pseudomonas aeruginosa*, *Streptococcus aureus* and *Klebsiella pneumoniae* and antifungal activity against *Candida albicans in vitro*. Besides, the extract exhibited potential *in vitro* anti-inflammatory activity via albumin denaturation and human red blood cells membrane (HRBC) stabilization assays.[72]

The aqueous extract of *P. wallichiana* stems was found to be non-toxic and non-mutagenic at all tested doses (up to 80 mg/kg) using the Ames and acute toxicity assays (Khan *et al*., 2020). Moreover, silver nanoparticles incorporating the water extract were significantly active against *Acinetobacter baumannii,* an opportunistic pathogen known to cause wound and surgical site infections, especially in individuals with immune system deficiencies.[73]

P. roxburghii offers a similar profile and opportunities.

Valeriana jatamansi Jones ex Roxb.

Valeriana jatamansi is distributed from Eastern Afghanistan to Central & East Central China but also in Eastern China. Rhizomes, roots and the whole plant of this species have been used in four countries for the treatment of cuts and wounds, boils, pimples, pus or abscesses and other skin diseases (Supplementary Appendix S1). The species should not be confused with *N. jatamansi*, see above.

Valeriana jatamansi rhizomes' aqueous and methanolic extracts considerably reduced inflammation of carrageenan-induced paw oedema in rats by inhibiting the production of inflammatory mediators histamine, prostaglandin and serotonin.[74] This could be linked to the presence of iridoids, including a series of jatodamines (A to E), and the sesquiterpenoid 8-acetoxyl-pathchouli alcohol inhibiting nitric oxide release in LPS-induced murine microglial BV-2 cells. However, the latter model is not directly relevant for skin conditions and is, in pharmacological terms, very preliminary. Patan *et al*.[74] also reported the antibacterial potential of hydro-alcoholic extracts of *V. jatamansi* extracts, at doses of 0.3–0.7 mg/ml, on *S. aureus*, *P. aeruginosa*, comparable with chloramphenicol used at 1 mg/ml. Valerenic acid was responsible for the antibacterial activity.

Valeriana jatamansi is often confused with the endangered *N. jatamansi* (as mentioned earlier). Consequently, *V. jatamansi*, is considered potentially at risk, too[70] and for this reason may not be a good lead species.

Conclusion

In our approach, we used a multi-step process to identify potential lead species for the future development of effective, safe and cheap treatment regimens for infected wounds that rely on the activating power of light. After an initial screening of the literature, we focussed on species that are more likely to be exposed to intensive levels of light, because they may produce more bioactive substances, which are light-sensitive.

The approach has some important limitations. The available information on the distribution of species does not allow a clear-cut differentiation of species between high mountain and other regions. Therefore, further analysis of these species may be needed. Also, the number of species restricted to high mountain regions is relatively low (ca 25%). People living in the region clearly use what they have access to and thus we identified a large number of common if not ubiquitous species. This finding, in fact, provides further evidence that people's choice of medicines is driven by accessibility and thus the level of distribution (and weediness) of a species affects the frequency of use. At the same time, some of these species may well be of pharmacological interest, since they have been able to adapt to challenging and diverse ecological conditions and are used globally. Of course, this is a preliminary analysis identifying lead species and, at this stage, much more evidence is needed to identify potential benefits, limitations and specific risks. Ingenol 3-angelate (s) provides a good example of the level of research needed. It was first seen as an excellent treatment of treating actinic keratoses and non-melanoma skin cancer. After its introduction in 2012, the marketing authorization was withdrawn in Europe in 2020 due to reported carcinogenicity[75] indicating that a very robust level of evidence will need to be created.

In a next step and once sustainable sourcing based on full access and benefit-sharing arrangements is in place, these species could be investigated for their potential in wound treatment. Ultimately, the goal is to develop a new baseline for primary health care in some of the poorest regions of the world.

The strategy used here proposes a new combination of ethnopharmacological and phytogeographical approaches with innovative treatments and, as such, offers new opportunities for drug development, in this case for skin diseases. The combination has the potential to contribute to novel basic research into long-sought sustainable methods to promote wound healing while preventing or even treating local infections effectively, safely, at low cost and in an outpatient setting. Especially for people with lower or very low income and limited access to basic or standard health provision, this may provide a very high-impact, affordable primary care option. While strictly adhering to principles of Access and Benefit Sharing as defined in the Nagoya Protocol,[76] it also strongly contributes to the Sustainable Development Goals of the United Nations.[77]

Supplementary Material

Supplementary data are available at *Journal of Pharmacy and Pharmacology* online.

The citations for references [78-152] are available in Supplementary Appendix S1.

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Authors Contributions

M.H. designed the study and supervised the project including an MSc dissertation by H.J., who gathered the data and provided an analysis. F.S. and A.B. contributed aspects esp. relating to plant sciences and ethnopharmacology, C.W. on the taxonomy and botany, H.W. and C.M. on photodynamic aspects. All authors read the MS and approved the final version.

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Conflict of Interest

None declared.

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