An Insight into Antioxidant and Antimicrobial Activities of Ethnotherapeutically Important Trans Himalayan Medicinal Plants: A Review

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Authors' contributions

This work was carried out in collaboration among all authors. Author ASA designed the study and collected the relevant material. Author NK analyzed the collected literature and wrote the first draft. Author SS managed the analyses of the study. Author SG finally reviewed and critically drafted the final draft. All authors read and approved the final manuscript.

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ABSTRACT

The high altitude of the Himalayan cold desert represents a valuable habitat of natural resources. The extreme climatic condition manifested by intense mutagenic UV-radiation, physiological drought, desiccation and strong winds, makes the survival of plants really difficult. As a consequence of this atmospheric stressor, the plants produce unique metabolites which play a preventive role in intrinsic mechanism of sustenance. Many plant species of this region have been investigated in search of novel antioxidants and antimicrobials. Plants synthesize several antioxidants that aid in antioxidant defense system, thereby protecting plants against damage caused by active ROS. These compounds include chlorophyll derivatives, alkaloids, essential oils, phytosterols, phenolics and polyphenolics. Some of the antioxidants that have been isolated from plants include curcumin, quercetin, ascorbic acid, resveratrol amongst many other compounds. Additionally, the emergence of resistance to multiple antimicrobial agents has become a major threat to public health. Hence, fresh efforts towards new drug identification and development are greatly needed. Plants have long been used in traditional Indian medicine for numerous therapeutic
benefits and low toxicity. Considering the growing interest in quest for search of plant based antimicrobials and antioxidants; an effort has been carried to systematically record the antioxidants and antimicrobial potential of plants of Himalayan region.

Keywords: Trans-Himalayan region; secondary metabolites; antioxidant; antimicrobial; phenolics; flavonoids.

1. INTRODUCTION

The northern part of India, especially Himalayan terrain is a hot spot of medicinal plants. In particular, Indian Trans-Himalayan mountain range supports low vegetation cover due to harsh climatic conditions along with short growing season. More than 8000 species of angiosperms, 44 species of gymnosperms and 600 species of pteridophytes have been reported from the Indian Himalayas, and of these, 1748 species are known for their therapeutic potential [1]. The high altitudes of the Himalayan cold desert represent a valuable habitat of natural resources. The extreme climatic condition manifested by intense mutagenic UV-radiation, physiological drought, desiccation and strong winds, makes the survival of plants really difficult. As a consequence of this atmospheric stressor, the plants produce unique metabolites which play a preventive role in intrinsic mechanism of sustenance [2]. However, high altitude medicinal plants (HAMP) are amongst the least well studied organisms of terrestrial ecosystems. This is largely due to misconceptions about poor biodiversity, small number of individuals per species, reduced surface inaccessibility, and relative simplicity of these habitats. These plants are capable of growing successfully at altitudes surpassing 5000 m mainly because of specialized physiological processes that include synthesis of special lipids which alter the flexibility and water permeability of cell membranes, anti-freeze carbohydrates and other unique secondary metabolites [3,4]. These conditions induce the biosynthesis of UV protection and free radical scavenging compounds in these plants.

From this Trans Himalayan region, 414 species of higher plants covering 56 families and 202 genera have been recorded. Almost a quarter of the recorded species (102 species) are reported to be used in traditional system of medicine whereas over 80 species are largely associated with cultivated fields and human habitation. These also include 49 species of crop plants like barley and buckwheat [4]. The local medical practitioners of this region, Amchis, use local herbs either as extract or sometimes in combination with salts or minerals and these concoctions are well acclaimed for their

Fig. 1. Map of Trans Himalayan region of India
medicinal values for many disorders like memory loss, osteoporosis, age related disorders, AIDS and cancer [5]. This traditional knowledge is not only useful for local health care, but also for the conservation and sustainable use of medicinal plants. This knowledge has been slowly diminishing due to the changing socio-economic circumstances of the region, but there has been a renewal and a revitalization of this ancient and time-tested tradition of healing in recent times. Considering the growing interest in quest for search of plant based antimicrobials and antioxidants; an effort has been carried to systematically record the antioxidants and antimicrobial potential of plants of this Trans Himalayan region.

2. METHODOLOGY

A systematic web search analysis and review was conducted on research literature pertaining to medicinal plants from Trans Himalayan region of India with reported biological activities. The search engines used for retrieving published data (from 2000 to 2020) include universally recognized databases, specifically, Scopus, PubMed, ScienceDirect, and Google Scholar. The search strategy was to retrieve and download published literature dealing with medicinal plants and compounds having antibacterial and antioxidant activities. Specific keywords such as “Trans Himalyan”, “antioxidant”, “antimicrobial” and “in vitro or in vivo activity”. Studies reporting in vitro/in vivo efficacy of medicinal plants were included in this review.

3. PLANTS REPORTED WITH ANTIOXIDANT ACTIVITY

It is well established that plants have an innate ability to synthesize wide variety of non-enzymatic antioxidants which are capable of mitigating reactive oxygen species (ROS) induced oxidative damage. These antioxidants can delay or prevent the oxidation of various intracellular oxidizable substrates even at significantly lower concentrations than that of the substrate. It is believed that two-thirds of the available plants on this earth have at least some medicinal importance, and majority of them possess significant antioxidant potential [6]. The interest in the exogenous plant derived antioxidants was first aroused by the discovery and subsequent isolation of Vitamin C (ascorbic acid) from plants. Since then, the antioxidant potential of plants has received a boundless attention because increased oxidative stress has been recognised as a major causative factor in the development and progression of many life-threatening disorders, including neurodegenerative and cardiovascular diseases [7]. This antioxidant activity is mostly credited to the presence of phenolic acids, phenolic diterpenes, flavonoids and volatile oils as secondary metabolites in plants. Some plant pigments like anthocyanin also possess antioxidant activity [8]. For each of these metabolites, a distinct mechanism of action is followed which may include decreasing localized oxygen concentration in the tissues, preventing chain initiation by scavenging radicals, disintegrating lipid peroxides to peroxyl and alkoxyl radicals; decomposing peroxides by altering them to non-radical products or by terminating the free radical propagation to prevent sustained hydrogen abstraction [9].

The most effective antioxidants are those which can interrupt free radical chain reactions, which starts under various stress conditions. They usually contain phenolic or aromatic rings and can donate hydrogen atom to the free radicals formed during oxidation (Fig. 2). The freshly formed phenolic radical intermediates are stabilized by resonance within the aromatic ring [10].

![Stable phenoxyl radical](image)

*Fig. 2. Antioxidant activity of phenolic compounds*
Fig. 3. Mechanism of antioxidant activity of flavonoids

Phenols (ArOH) donate H to scavenge the reactive free radical. They in turn gets converted into phenoxyl radical (ArO·). The phenoxyl radical is stabilised by resonance.

Phenolic compounds are also capable of suppressing lipid peroxidation by recycling other endogenous antioxidant Vitamin E (a-tocopherol). They can also bind to pro-oxidant metals, such as iron or copper and hence prevent the formation of free radicals [11]. They are also reported to induce synthesis of antioxidant proteins including antioxidant enzymes like SOD and CAT [12].

Similarly, flavonoids can also donate hydrogen and in turn forms stable flavonoid semiquinone radicals, which may later be scavenged by intracellular antioxidant glutathione (GSH, reduced state). The ratio of intracellular reduced glutathione to oxidized glutathione is often used measure of cellular oxidative stress. Glutathione acts as an electron donor to reduce the disulfide bonds formed within cytoplasmic proteins to cysteines. In the process, glutathione is converted to its oxidized form, glutathione disulfide (GSSG, oxidized state) [13] as depicted in Fig. 3. Once oxidized, the GSSG can be reduced back to GSH by another enzyme GR (glutathione reductase) that uses NADPH as an electron donor.

A flavonoid compound donates H to scavenge free radicals and gets converted to a stable flavonoid free radical. This radical is scavenged by intracellular non-enzymatic antioxidant glutathione (GSH).

Since flavonoids contain multiple hydroxyl groups, they are considered more effective antioxidants. The presence of the ortho- 3, 4-dihydroxy moiety further enhances the antioxidant activity of these secondary metabolites [14]. Additionally, flavones and some flavanones can favourably bind to prooxidant metals thus rendering them ineffective [15]. Apart from number and position of OH groups, it is the ability to partition between the lipid and hydrophilic phase also plays an important role in the bioactivity of these compounds. Compounds that are capable of correctly orienting at the interphase of oil droplet in emulsion can act as a better inhibitor of ROS induced lipid peroxidation [16].

4. PLANTS REPORTED WITH ANTIMICROBIAL ACTIVITY

Beside antioxidant potential plant secondary metabolites also exhibit multiple pharmacological activities including anti-inflammatory, antimicrobial, anti-cancer etc. Also, they play significant role in self-defence and ecology [17]. Bacterial species also have genetic ability to acquire and subsequently transfer resistance to subsequent generations against currently available antibiotics/antibacterial agents, thus, becoming multi-resistant to the commercially available medications [18]. Hence, as a substitute to commercially used antimicrobial drugs, bioprospecting of plants as a source for new and safe antimicrobials is now being explored globally. Antimicrobial properties in plants are also credited to the presence of bioactive secondary metabolites. Plant derived antimicrobial peptides are also a part of plant defense systems and these are analogous to human antimicrobial peptides in their structure and function [19]. The mode of action of these
natural plant derived antimicrobials include disintegration of cytoplasmic membrane, destabilization of the mitochondrial proton motive force (PMF), disruption of electron flow and ATP based active transport and coagulation of the cellular content [20].

Here, we present a few important classes of plant derived secondary metabolites with well-established antimicrobial potential for example quinones, alkaloids, flavonoids, coumarins, essential oils, tannins, lignans, glucosinolates and thionins.

Quinones are a class of compounds which possess fully conjugated cyclic dione structure, example benzoquinones. They are capable of binding to the bacterial cell wall and also inhibit key bacterial enzymes [21]. Lawsonia inermis, commonly known as henna, also contains quinones exhibiting antibacterial activity against Pseudomonas aeruginosa [22]. Quinone rich extract of Hypericum perforatum, has demonstrated general antimicrobial properties and has also been found to be active against meticillin-resistant and meticillin-sensitive Staphylococcus [23].

Another group of plant metabolites are alkaloids which contain a basic nitrogen atom. This group also comprises of some other related compounds which have neutral or weakly acidic properties. Their occurrence is common in angiosperms. The pharmacological importance of alkaloids was first recognized with the isolation of morphine from Papaver somniferum. Since then, many medicinally important alkaloids have been reported viz., berberine, caffeine, quinine, codeine, strychnine, ephedrine, emetine and narcotine. Many plant species like Berberis spp., Cortex phellodendri and Rhizoma coptidis have shown significant antimicrobial activity due to the presence of high concentrations of alkaloids in their extracts [24]. However, these compounds are not frequently used in folk medicine due to their associated toxic effects at higher concentrations.

Chemical structure of flavonoids can be abbreviated as C6-C3-C6 containing two phenyl rings and one heterocyclic ring. Flavonoids are widely distributed in plant kingdom [8]. They are also abundant in many plant products like honey, fruits, seeds, vegetables, wines and tea. Beside antioxidant activity, a number of flavonoids also possess antimicrobial, antiviral, antiallergic and anti-inflammatory properties [25]. Few flavonoids have shown significant antifungal activity against Botrytis cinerea and Aspergillus flavus [26]. Flavonoids from Galium fissurense, Viscum album ssp. album and Cirsis hystoecicum have been reported to have antibacterial activity against extended-spectrum β-lactamase, producing multidrug-resistant bacteria Klebsiella pneumoniae [27]. These compounds are able to bind to bacterial cell wall causing membrane disruption of the pathogenic organism [21].

Coumarins are phenolic secondary metabolites of benzopyrone chemical class, containing fused benzene and an alpha pyrone ring [28]. Extract of Ferulago campestris containing pyranocoumarins possess antibacterial activity against many Gram-positive and Gram-negative clinical isolates [29]. Similarly, coumarins from Angelica lucida L. have been found to be active against Streptococcus mutans and S. viridians, causative agents of oral cavity and dental infections [30].

Essential oils are present in almost all plants and are the largest group of plant derived secondary metabolites. This class constitutes mainly of a number fatty acids/esters and lower homologues of terpenoids. These oils often possess sweet aroma. Five carbon isoprene unit is the building block of all terpenes. When a terpene molecule contains an additional functional group they are called terpenoids. In general, terpenoids are reported to be active against bacteria, fungi, viruses, and protozoa. Some widely prevalent terpenoids with antimicrobial properties include menthol, citral, camphor, salvinorin A and cannabinoids. They are generally amphipathic and hence are able to cause membrane disruption in the target organisms [21].

Tannins are a class of polyphenolic compounds containing large number of - OH and other functional groups like –COOH to form strong complexes with various macromolecules. The tannin compounds are also widely distributed in many plant species e.g., red wine and green tea, where they play a role in defense against microorganisms and pests. The tannin from Sorghum species had been active against S. aureus, Salmonella typhimurium, A. niger, A. flavus and Saccharomyces cerevisiae [31].

Lignans are a group of dimeric-phenylpropanoids formed by fusion of two cinnamyl alcohol/cinnamic acids via the β-carbon of the aliphatic chain. Some plant derived lignans also
possess antimicrobial activity e.g., lignans from *Pseudo larixkaempferi* were found to be active against *Candida albican* and *S. aureus* [32].

Glucosinolates present in many species of Brassicaceae family are sulphur and nitrogen containing secondary metabolites. They are abundant in broccoli, mustard and Brussels sprouts and have antifungal, antimicrobial, anticancer, antioxidant and anti-inflammatory activity [33].

Thionins are a group of small proteins found solely in higher plants. They have disulphide bonds and are positively charged. The positive charge of these thionins (antimicrobial peptides) can bind to negatively charged membrane constituents like phospholipids, teichoic acid and lipopolysacharide, and can disrupt membrane structure and result in death of the bacterial cell. For example fabatin which has been extracted from the fava beans contains 47 peptide residues that have shown antimicrobial activity against *P. aeruginosa* and *E. coli* [34].

**5. ADAPTATIONS OF PLANTS IN NATURAL HABITAT OF HIMALAYAS**

The plants of Himalayas are extremely specialized group that have metabolic and propagative adaptations suited for maximizing their activity under adverse harsh climatic conditions [35]. They exhibit many ecological, morphological and physiological adaptations which help them to offset the impact of severe climate prevailing in this area. They have developed a very deep and extensive root system which can absorb water even from great depth, and can also endure strong winds, snow blizzards and thus help in preventing damage due to prevalent subzero temperature during winter season. Another survival mechanism for these plants is the underground modified stem or rhizome and bulbs which help in the survival of the perennial herbs in harsh winters. The major physiological adaptation in these plants, however, is their resistance to frost, either through inhibition or reduction in the ice crystal formation. Due to short growing season, these plants have to complete their entire life cycle starting from seedling growth to sprouting of leaves and flowers, fruiting and dispersal of seeds in a span of few months. This is promoted through reproduction being carried out both by sexual as well as vegetative methods [36].

**6. RESULTS AND DISCUSSION**

The plants of Ladakh Himalaya are exposed to severe environmental stress which manifests in the production of high content of secondary metabolites. This has also been established that antioxidant potential of these plants is comparable and even greater than established commercially available antioxidant extracts like green tea and Indian gooseberry. Extracts of *Pyrus pashia*, *Ephedra gerardiana*, *Salvia sclarea*, *Gentiana spp*, *Potentilla fruticose*, *Rheum austral* collected from this region showed significant antioxidant property with IC$_{50}$ values less than 30μg/mL (DPPH) indicating promising free radical scavenging ability. The antioxidant activity is comparable to honey, a well-known dietary antioxidant that contains phenolic acids, flavonoids, vitamins, and enzymes. The Total phenolic content of honey is highly variable but can range from 100-200 mg GAE/g. The antioxidant activity measured by DPPH free radical scavenging ranging from 29-64 μg/mL (IC$_{50}$ values) [74].

Some of the commercially important compounds having antioxidant activity include quercetin, ascorbic acid (Vitamin C) and tocopherol (Vitamin E). These compounds showed similar IC$_{50}$ 9.479, 15.62, 11.23 μg/ml respectively, measured by DPPH assay [75-77]. In addition to high radical scavenging activities, few extracts also induced antioxidant defence systems by enhancing GST and SOD levels e.g., *Podophyllum hexandrum*. Hence these plants can reduce the free radicals induced oxidative damage through multi-functional approaches.

The plants of this region also possess significant antimicrobial activity against human pathogens. MIC values of 50μg/mL have been reported for *Pholidota articulata* against enteric pathogen *Salmonella entericitaphym*. Similarly *Dioscorea deltoidea* and *Arnebia benthamii* extracts exhibited MIC of 50 and 62.5μg/mL respectively against *P. aeruginosa*, which is considered to be a resistant organism. *Euphorbia wallichii* and *Valeriana wallichii* also demonstrated lower MIC values against *Staphylococcus aureus* and *Bacillus subtilis*. It is significant to note that antimicrobial activity is not restricted to a specific class of microbes but against both Gram positive and Gram negative bacteria as well as pathogenic fungi *Microspoum canis*, *Fusarium*
| Species                | Family            | Location                       | Part/Extract/Fraction   | Activity tested                  | Values                                      | Ref.   |
|-----------------------|-------------------|--------------------------------|-------------------------|-----------------------------------|---------------------------------------------|--------|
| *Dracocephalum*       | Lamiaceae         | Himalayan region of Ladakh     | methanolic extract      | DPPH                              | IC$_{50}$ of 37 μg/mL                      | [37]   |
| *heterophyllum*       | Benth.            |                                |                         |                                   |                                             |        |
| *Rumex patientia*     | Polygonaceae      | Himalayan region of Ladakh     | acetone extract         | TPC, TFC, DPPH, ABTS and FRAP     | TPC value of 803mg GAE /100 g fresh weight, IC$_{50}$ DPPH (0.99 mg/ mL), ABTS (1.37 mg/ mL) and FRAP (0.261 mg/ mL) DPPH IC$_{50}$ of 2.306μg/ mg, 385.76 mM FeSO4.7H$_2$O | [38]   |
| *Saussurea lappa*     | Asteraceae        | Himalayan region of Ladakh     | 80% methanol extract    | DPPH, FRAP                        |                                             | [39]   |
| *Arnebia euchroma*    | Boraginaceae      | Himalayan region of Ladakh     | 80% methanol extract    | TPC, TFC                          | 244.58μg GAE/mg, 17.77μg QE/mg             | [39]   |
| *Inula racemose*      | Asteraceae        | Himalayan region of Ladakh     | 80% methanol extract    | Flavonol content                  | 70μg QE/mg                                 | [39]   |
| *Rhododendron*        | Ericaceae         | Himalayan region of Ladakh     | 80% methanol extract    | Proanthocyanidin content          | 108.33μg QE/mg                            | [39]   |
| *webbanium*           |                   |                                |                         |                                   |                                             |        |
| *Pyrus pashia*        | Rosaceae          | Himalayan region of Northeastern India | leaf- methanol extract | TPC, DPPH                         | 356.47 mg/g GAE, DPPH IC$_{50}$ of 28.97 µg/ml | 40     |
| *Oenanthe javanica*   | Apiaceae          | Himalayan region of Northeastern India | shoot- methanol extract | TPC, DPPH                         | 36.42 mg/g GAE, , DPPH IC$_{50}$ of 94.00μg/mL | [40]   |
| *Maianthemum*         | Asparagaceae      | Himalayan region of Northeastern India | shoot- methanol extract | TPC                               | 19.82mg/g GAE                              | [40]   |
| *purpureum*           |                   |                                |                         |                                   |                                             |        |
| *Ephedra gerardiana*  | Ephedraceae       | Himalayan region of Ladakh     | leaf – ethanol extract  | DPPH                              | IC$_{50}$ of 13.30 μg/mL                   | [41]   |
| *Salvia sclarea*      | Lamiaceae         | Himalayan region of Ladakh     | flower – ethanol extract| DPPH                              | IC$_{50}$ of14.97µg/mL                     | [41]   |
| *Senecio amplexicaulis*| Asteraceae        | Himalayan region of Uttarakhand | oil                     | DPPH, ABTS, Lipid peroxidation    | DPPH IC$_{50}$ value of 81.6µg/mL, Inhibition of 44.8% of the | [42]   |
| Species                          | Family           | Location                        | Part/Extract/Fraction | Activity tested | Values                                                                 | Ref. |
|---------------------------------|------------------|---------------------------------|-----------------------|-----------------|-------------------------------------------------------------------------|------|
| *Gentiana spp*                  | Gentianaceae     | Himalayan region of western and central Himalayas | aerial part           | DPPH            | 71% inhibition of lipid peroxidation at 100 μg/mL IC50 value of 13.6 μg/mL | [43] |
| *Rheum australe*                | Polygonaceae     | Himalayan region of western and central Himalayas | aerial part           | DPPH            | IC50 value of 18.9 μg/mL                                                 | [43] |
| *Hippophae rhamnoides*          | Elaeagnaceae     | Himalayan region of Ladakh      | flavonoid rich fraction, seeds, stem bark | Peroxy radical scavenging, FRAP, DPPH | 64.82 % scavenging, 12.61 mM FeSO4, IC50 ranges from 0.7 to 9.1 mg/mL for different parts | [44, 45] |
| *Podophyllum hexandrum*         | Berberidaceae    | Himalayan region of Ladakh      | rhizome aqueous extract | GST (Glutathione S-transferase), CAT (catalase), SOD (superoxide dismutase) activities and lipid peroxidation (LPx) | Enhancement in GST and SOD levels, No significant change in catalase level. | [46] |
| Phytococktail of *Hippophae rhamnoides, Prunu sarmeniaca and Rhodiola imbricata* | -                | Himalayan region of Ladakh      | methanolic and n-hexane extracts | DPPH IC50 value of 393.5 and 319 μg/mL, FRAP of 8.21 × 10⁻³ and 1.03 X 10⁻³ mol Fe (II)/g, TPC 2.3 X 10⁻⁴ and 2.89 X 10⁻⁴ mol/g GAE, TFC 4.21 X 10⁻⁶ and 6.11 X 10⁻⁵ mol QE respectively for methanol and n-hexane extract | TPC 270 mg, 240 mg and 110 mg GAE/g, TFC 65,20 and 85μg QE/g, for | [47] |
| *Eremurus Himalaicus*           | Asphodelaceae    | North Western Himalayas (Kashmir) | methanol, ethylacetate and aqueous extracts | TPC, TFC, DPPH and H₂O₂ scavenging | TPC 270 mg, 240 mg and 110 mg GAE/g, TFC 65,20 and 85μg QE/g, for | [48] |
| Species               | Family         | Location                        | Part/Extract/Fraction | Activity tested       | Values                                                                 | Ref.  |
|----------------------|----------------|---------------------------------|-----------------------|-----------------------|--------------------------------------------------------------------------|-------|
| Capparis spinosa     | Capparaceae    | Himalayan region of Ladakh      | aerial part           | TPC, TFC, DPPH, ABTS and FRAP | TPC 27.62-21.42 mg GAE/g DW and TPC 6.96-2.69 mg QE/g DW methanol, ethylacetate and aqueous extracts respectively. IC$_{50}$ value of 148.1788 and 182.3371μg/mL for DPPH and H$_2$O$_2$ scavenging respectively. | [49]  |
| Potentilla fruticosa | Rosaceae       | Himalayan region of Tibet       | aerial part           | DPPH, FRAP            | DPPH IC$_{50}$ value of 9.2 μg/mL, FRAP 416.6 μmol equiv. Trolox/g.     | [50]  |
| Olea ferruginea      | Oleaceae       | Trans Himalayan region of Himachal Pradesh | mature fruits, methanolic extracts | TPC, DPPH, ABTS | 2.30-3.41 TAE/g fw, IC$_{50}$ value of 0.15 - 0.24mg/ml, 0.0019 - 0.0138 AAE/g fw | [51]  |
| Picrorhiza kurroa     | Plantaginaceae | Trans Himalayan region of Ladakh | whole plant           | DPPH, ABTS            | IC$_{50}$ value of 67.48μg, 48.36μg respectively                         | [52]  |
| Potentilla fulgens   | Rosaceae       | Western Himalayas               | roots                 | ABTS, DPPH, FRAP      | 2.54, 2.41 and 3.57 mM TE/mg respectively                                | [53]  |
| Acorus calamus       | Aracacerae     | Uttarakhand Himalayas           | rhizome               | TPC, ABTS             | 7.35 mg GAE/g, 23.28 mM AAE/100g respectively                             | [54]  |
| Habenaria intermedia | Orchidaceae    | Uttarakhand Himalayas           | rhizome               | TPC, ABTS, FRAP       | 2.74 mg GAE/g, 7.48 mM AAE/100g, 10.59 mM AAE/100g respectively         | [54]  |
| Hedychium spicatum   | Zingiberaceae  | Uttarakhand Himalayas           | tuber                 | TPC, TFC              | 3.39 mg GAE/g, 6.85 mg QE/g respectively                                | [54]  |
| Roscoea procera      | Zingiberaceae  | Uttarakhand Himalayas           | rhizome               | TPC, ABTS, DPPH       | 19.10 mg GAE/g, 13.71 mM AAE/100g, 12.13 mM AAE/100g respectively       | [54]  |
| Valeriana jatamansi  | Valerianaceae  | Uttarakhand                     | roots                 | TPC, ABTS             | 12.82 mg GAE/g, 77.17                                                   | [54]  |
| Species                  | Family            | Location                          | Part/Extract/Fraction | Activity tested     | Values                                      | Ref. |
|-------------------------|-------------------|-----------------------------------|-----------------------|---------------------|---------------------------------------------|------|
| *Mentha longifolia*     | Lamiaceae         | Himalayan region of Ladakh        | whole plant, methanolic and acetone extract | TPC, DPPH           | mM AAE/100 g respectively                    | [55] |
| *Allium schoenoprasum*  | Amaryllidaceae    | Himalayan region of Ladakh        | whole plant, methanolic and acetone extract | ABTS                | 96.2 mg GAE/g dry wt., DPPH IC<sub>50</sub> value of 39.2 µg/mL | [55] |
| *Carum carvi*           | Apiaceae          | Himalayan region of Ladakh        | whole plant, methanolic and acetone extract | ABTS                | IC<sub>50</sub> value of 78.0 µg/mL        | [55] |
| *Origanum vulgare*      | Lamiaceae         | Himalayan region of Ladakh        | whole plant, methanolic and acetone extract | ABTS, DPPH          | IC<sub>50</sub> value of 18.8 and 25 µg/mL  | [55] |
| *Urtica hyperborean*    | Urticaceae        | Himalayan region of Ladakh        | whole plant, methanolic and acetone extract | TPC, TFC, DPPH      | 42 mg GAE/ g dry wt. and 4.0 mg QE/g, IC<sub>50</sub>value of 50 µg/mL respectively | [55] |
| *Hypericum perforatum*  | Hypericaceae      | Higher reaches of Gulmarg (J&K, India) at an altitude of 2600 m | leaves | TPC, TFC | 21.90 mg GAE/g and 17.10 mg RE/g respectively | [56] |
| *Arnebia benthamii*     | Boraginaceae      | Duksum and Sinthan Top, Kashmir Himalaya | aerial and roots | DPPH and lipid peroxidation | IC<sub>50</sub> value of 50 µg/ml, 72% inhibition of lipid peroxidation at 300 µg/mL | [57] |
| *Primula denticulata*   | Primulaceae       | Gulmarg region, Kashmir Himalayas | leaves, ethanolic extract | DPPH, H<sub>2</sub>O<sub>2</sub> scavenging, DNA protection | IC<sub>50</sub> value of 300 µg/mL for DPPH and H<sub>2</sub>O<sub>2</sub> scavenging, | [58] |
| *Bistorta macrophylla*  | Polygonaceae      | Tungnath, Chopta, Uttarakhand     | whole plant            | TPC, TFC, DPPH      | 76.14 mg GAE/ g, 51.55 GA/g, IC<sub>50</sub>value of 58µg/mL for DPPH respectively | [59] |
| *Bistorta*              | Polygonaceae      | Tungnath, Chopta, Uttarakhand     | whole plant            | TPC, TFC, DPPH      | 54.57 mg GAE/ g, 49.05                       | [59] |
| Species                  | Family            | Location            | Part/Extract/Fraction | Activity tested | Values                                                                 | Ref. |
|-------------------------|-------------------|---------------------|-----------------------|-----------------|------------------------------------------------------------------------|------|
| Vaccinifolia            |                   | Chopta, Uttarakhand | GA/g, IC₅₀ value of 70μg/mL for DPPH respectively |                 | Re: Rutin equivalent; TAE: Tannic acid equivalent; TPC: Total phenolic content; TFC: Total flavonoid content; QE: Quercetin equivalent; SOD: Superoxide dismutase; GST: Glutathione-S-Transferase |
| Persicaria polystachya  | Polygonaceae      | Tungnath, Chopta    | whole plant           | TPC, TFC, DPPH  | 67.42 mg GAE/g, 43.16 GA/g, IC₅₀ value of 60μg/mL for DPPH respectively | [59] |
| Pholidota articulata    | Orchidaceae       | RudraprayagUttarakhand | whole plant, ethylacetate extract | Salmonella enterica typhi (ZOI 16 mm, MIC 50μg/mL), Escherichia coli (ZOI 14 mm), Klebsiella pneumoniae (ZOI 18 mm) at 10 mg/mL | [60] |
| Senecio chrysanthemoides| Asteraceae        | RudraprayagUttarakhand | whole plant, ethylacetate extract | S. enterica typhi (ZOI 17 mm, MIC 50μg/mL), E. coli (ZOI 19 mm), K. pneumoniae (ZOI 13 mm), Aspergillus parasiticus (ZOI 8 mm) at 10 mg/mL | [61] |
| Cordyceps sinensis      | Clavicipitaceae   | Western Himalayas   | whole plant           | E. coli, P. aeruginosa and B. subtilis giving 9, 7 and 6.5 mm of zone of inhibition (ZOI) in 93.75, 93.75 and 45 μg concentration | [62] |
| Dioscorea deltoidea     | Dioscoreaceae     | Chamoli Uttarakhand | tuber                 | P. aeruginosa (MIC 50μg/mL), ZOI of 19 mm, 17 mm and 15 mm against S. aureus, P. aeruginosa and E. coli | [63] |
| Colocasia esculenta     | Araceae           | Uttarakhand Himalayas | leaves, aqueous extract | ZOI of 10 mm against S. mutans and K. pneumoniae           | [64] |
| Hypericum perforatum    | Hypericaceae      | Higher reaches of Gulmarg, Kashmir Himalayas | leaves | ZOI of 19.33 mm and 18.00 mm against B. subtilis and S. aureus respectively at the test concentration of 50 mg/mL | [56] |
| Euphorbia wallichi      | Euphorbiaceae     | High altitude region of Kashmir | root, aerial part, hexane extract | MIC of 128μg/mL against S. aureus | [65] |

Table 2. The Himalayan plants reported to possess antimicrobial activity
| Species               | Family         | Location                  | Part/Extract/Fraction | Activity against (Values)                                                                 | Ref. |
|----------------------|----------------|---------------------------|-----------------------|------------------------------------------------------------------------------------------|------|
| *Valeriana wallichii*| Valerianaceae  | Himalayas Uttarakhand     | aerial parts          | ZOI of 18 mm against *B. subtilis* (MIC 125 μg/ml), 15 mm against *E. coli* and 12 mm   | [66] |
|                      |                | Himalayas                 |                       | against *S. aureus* for hexane extract                                                    |      |
| *Centratherum         | Malvaceae      | Uttarakhand Himalayas     | seeds, chloroform     | MIC of 0.0020 μg/ml against *E. coli*, 0.025 μg/ml against *Colletotrichum*               | [67] |
| *anthelminticum*      |                |                           | extract               | *gloeosporioides, Phomopsis dalbergiae, Trichoderma piluliferum*                          |      |
| *Nepeta leucophylla*  | Lamiaceae      | Uttarakhand Himalaya      | aerial parts, oil     | ZOI of 20.0 mm and MIC = 0.78 μL/mL against *C. ablicans*, ZOI of 27.4 mm, MIC = 0.42 μL/mL | [68] |
|                      |                |                           |                       | against *P. aeruginosa*                                                                  |      |
|                      |                |                           |                       | ZOI of 21.2 mm, MIC = 3.21 μL/mL; 16.4 mm; MIC = 1.78 μL/mL against *P. vulgaris* and *S. aureus* |      |
| *Nepeta discolor*     | Lamiaceae      | Uttarakhand Himalaya      | aerial parts, oil     | ZOI of 18.2 mm, MIC of 1.42 μL/mL against *P. aeruginosa*                                | [68] |
| *Nepeta govaniana*    | Lamiaceae      | Uttarakhand Himalaya      | aerial parts, oil     | ZOI of 20.1 mm, MIC = 0.37 μL/mL against *P. aeruginosa*                                | [68] |
| *Nepeta clarkei*      | Lamiaceae      | Uttarakhand Himalaya      | aerial parts, oil     | ZOI of 22.0 mm, MIC = 0.15 μL/mL against *P. aeruginosa*                                | [68] |
| *Nepeta elliptica*    | Lamiaceae      | Uttarakhand Himalaya      | aerial parts, oil     | ZOI of 28.4 mm, MIC = 0.31 μL/mL against *P. aeruginosa*                                | [68] |
|                      |                |                           |                       | ZOI of 20.2 mm, MIC = 0.43 μL/mL against *S. marcescens*                                |      |
| *Nepeta erecta*       | Lamiaceae      | Uttarakhand Himalaya      | aerial parts, oil     | ZOI of 28.0 mm, MIC = 0.62 μL/mL against *P. aeruginosa*                                | [68] |
| *Arnebia benthamii*   | Boraginaceae   | Duksum and Sinthan Top,   | aerial parts and roots| MIC of 62.5 μg/mL against *P. aeruginosa*. MIC of 250 μg/mL against *Shigella flexneri* and *E.coli.* | [57] |
|                      |                | Kashimir Himalaya         |                       |                                                                                          |      |
| *Heracleum Lanatum*   | Apiaceae       | Gangotri, Uttarakhand     | aerial parts, oil     | MIC of 75 μL/mL against *S. aureus*, 125 μL/mL against *E.coli*, *P.aeruginosa* and *P. vulgaris*, 150 μL/mL against *Pichia guilliermondii*. | [69] |
| Species                        | Family            | Location                      | Part/Extract/Fraction     | Activity against (Values)                                                                 | Ref.  |
|-------------------------------|-------------------|-------------------------------|---------------------------|-------------------------------------------------------------------------------------------|-------|
| *Podophyllum hexandrum*        | Berberidaceae     | Kashmir Himalayas             | rhizome, methanolic and aqueous | ZOI of 9mm and 11 mm against *B. megaterium* and *P. aeruginosa* at 60 mg/mL. ZOI of 18mm and 15 mm against *A. flavus* and *F. solani* | [70]  |
| *Taxus wallichiana*            | Taxaceae          | Kashmir Himalayas             | leaf, bark, methanolic extract | MIC of 0.83 mg/mL against *E.coli*, 0.49 mg/mL against *S.aureus*, 0.42mg/mL against *S. typhi*, 0.78 mg/mL against *Microspoum canis*, and 0.11 mg/mL against *F. solani* | [71]  |
| *Primula denticulata*          | Primulaceae       | Gulmarg region, Kashmir Himalayas | leaves, ethanol extract | ZOI of 15.66 mm against *E.coli*, 11.44 mm against *K. pneumoniae* | [49]  |
| *Tanacetum longifolium*        | Asteraceae        | Milam glacier of Western Himalaya, Uttarakhand | whole plant, oil | ZOI of 22 mm against *E.coli* and 14 mm against *S. mutans* | [72]  |
| *Artemisia maritima*           | Asteraceae        | Keylong (H.P.) Himalayas,     | whole plant, oil          | MIC of 1.2 µL against *Pseudomonas fluorescence*, 2 µL against *B. subtilis*, 6 µL against *S. aureus*, 7 µL against *S. epidermis* and 9 µL against *Salmonella typhimurium* | [73]  |

*MIC: Minimum inhibitory concentration; ZOI: Zone of inhibition*
and Candida albicans. The antimicrobial potential of these plants is comparable to essential oils from clove (Syzygium aromaticum) and rosemary (Rosmarinus officinalis), both of which are commercially used in food with MIC ranging from 62.5 -500μg/ml against pathogenic Staphylococcus epidermidis, Escherichia coli and Candida albicans [78].

7. CONCLUSION

The plants of Ladakh, India are integral part of tribal diet, and are associated with many health protection benefits too. The literature search clearly showed that many plants of this region showed potential antioxidant and antimicrobial activities against human pathogenic bacteria in vitro. In addition, most of the antimicrobial and antioxidant active plants species are non-toxic. The results of this study suggest that extract of these species could be used as natural antioxidant to reduce free radical mediated disorders and may also be a source of active molecule against disease causing pathogens. Several antioxidant and antimicrobial compounds could be obtained from these plants resources. Therefore, further works of isolation and characterization of antioxidant and antimicrobial compounds merits from these plants resources.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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