

## Phytochemical potentials and medicinal uses of twenty-four selected medicinal plants from Swabi, Pakistan

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**Key Message** This study describes the valuable ethno medicinal information about the ethno botanicals. During this study, twenty-four medicinal plant species were documented as herbal medicines by the communities of Swabi, Pakistan.

**ABSTRACT** Poverty is persistent in district Swabi, Pakistan. A majority of the population cultivates small farms for its survival and earns extra money adopting small trade of medicinal plants collection to prepare the herbal medicines. The current study is based on ethno botanical data collection of the study area to document the valuable ethno medicinal information for the future generation. It is a qualitative study of 24 selected medicinal plants by field visits and questionnaire. Plants were collected from three study sites (research stations, plain areas and hilly areas). The hill stations were surveyed every fifteen days from January, 2010 to December, 2010. Change in temperature of selected site is negligible but human activities, grazing and soil texture verify the plant diversity. Plant species grow well in hilly site than that of plain areas. The results showed that among twenty-four medicinal plant species documented as herbal medicines by Swabi communities, the most familiar species included *Hordeum vulgare*, *Lantana camara*, *Melia azedarach*, *Mentha longifolia*, *Morus nigra*, *Nerium odorum*, *Nicotiana tabacum*, *Opuntia dillenii*, *Oxalis corniculata* and *Phaseolus lunatus*. During this study, it was found that ethnomedicinal information is transferred from generation to generation from older to younger people. This study provides a base line for developing plans so that these precious species can be preserved and used for drug production in future. Over exploitation by unscientific way of harvesting of these species should be controlled. Moreover, tissue culture techniques should be used to increase the production of these plants.

**Keywords:** Ethno botanicals, Folks, Natural products, Swabi-Pakistan, Traditional medicines

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### INTRODUCTION

Since the prehistoric times, plants have been used to protect human beings from serious diseases including cancer, neurodegenerative as well as microbial infections, because they possess various bioactive molecules which give multiple responses in various diseases (Napar et al., 2012; Ghali et al., 2014; Jan et al., 2015). They have not been only used as medicines but also provide the basic necessities of life such as shelter, clothing and food. The traditional system of medicines has been greatly improved by modern system of medicinal plants for the production of useful drugs. Ethno botanical study paved ways for the exploration of new classes of compounds (Gurib-Fakim, 2006). Medicinal plants provide sources of pharmaceuticals in order to treat diseases and hence their demand is increasing day by day. Trade initiated globalization of herbal medicines that unveiled the mystery of underlying metabolic mechanisms, novel ideas, diseases and settlements along with indigenous antipathy (Inoue & Craker, 2014). The common concern about production of medicinal

plants is progressively increasing every year at the domestic level. Due to more advanced techniques, the income levels have been increasing due to ample awareness among the growers about proper harvesting of medicinal plants. In the same way, research on natural products flourishes to make available plants in a sufficient quantity for the remedy of various diseases (Barnes et al., 2008; Oh et al., 2014).

From literature review, it has been found that the botanicals have been used conventionally for a long time to cure different forms of cancers but associated with fewer side effects as recorded in modern chemotherapy (Jung Park & Pezzuto, 2002; Cragg & Newman, 2005). Considering these potential benefits of plants as anticancer compounds, National Cancer Institute of USA conducted a detailed study on medicinal plants and collected 35,000 plant samples from twenty countries and evaluated 114,000 extracts for possessing anticancer activity (Shoeb, 2006). Prior to 1983, among ninety-two anticancer drugs marketed in USA were 60% of plant origins (Newman & Cragg, 2012).

The use of medicinal plants in Swabi is an alternative therapy which mainly depends upon indigenous knowledge obtained from ancestral experience. There is an important traditional botanical biography that describes the most frequently used plants in clinical conditions, but very few of them have been examined scientifically. However, the vast majority of botanicals have been still unexplored. Hitherto, their phytochemical and medicinal properties have not been validated. Keeping in view the above background, the present study was carried out to analyze taxonomic status, biochemistry and uses of twenty-four selected medicinal plants such as *Hordeum vulgare*, *Lantana camara*, *Melia azedarach*, *Mentha longifolia*, *Mentha viridis*, *Morus nigra*, *Nerium odorum*, *Nicotiana tabacum*, *Opuntia dillenii*, *Oxalis corniculata*, *Phaseolus lunatus*, *Plantago ovate*, *Prunus amygdalus*, *Psidium guajava*, *Ricinus communis*, *Rosa indica*, *Silybum marianum*, *Solanum nigrum*, *Solanum xanthocarpum*, *Tamarix gallica*, *Trigonella foenum-graecum*, *Verbascum Thapsus*, *Vicia sativa*, *Vitis vinifera* from district Swabi, Khyber Pakhtunkhwa Pakistan. This is the first report about the medicinal uses of these botanicals based on the information gathered from elder people in Swabi, Pakistan.

## **MATERIALS AND METHODS**

This research study was conducted in diverse areas of district Swabi, while the taxonomic and chemical constituent study was carried out at the laboratory of plant taxonomy, Abdul Wali Khan University, Mardan Khyber Pakhtunkhwa, Pakistan.

### **Medicinal plants survey**

Before starting the investigation survey, an executive letter was obtained from Abdul Wali Khan University, Mardan, Pakistan, while verbal consent was received from each participant. After thorough study of literature, the study trips were planned keeping in mind the blooming period of medicinal plants. Two different methods were followed during fields. In first method, observations were kept visiting different localities. In second method, questionnaire was made to collect data in different villages from the herbal physicians, local inhabitants, timber dealers and drug dealers to gain the information about the different medicinal plants. People of age group above 40 years and local herbalists were considered for data documentation because they knew well the actual uses of medicinal plants in their folk knowledge. Questionnaire having questions related to the local names, local uses, economic importance and other relevant information were conducted to collect data. The questions about uses of plants, rate of utilization, availability and their market values were also discussed with the local people.

### **Collection of medicinal plants**

The first trip was arranged to the plain areas of Swabi including Tarakai, Dagai, Ismaila, Zeda and Topai. Another trip was arranged to the hilly areas of Swabi including Sheraghund Hills, Naranje Hills and Shah Mansur Hills (Fig. 1). These study sites were chosen on the basis of information collected from traditional healers, community elders and health workers. During the medicinal plants collection, 3-5 specimens per plant were collected and their photographs were captured.

## Medicinal plants preservation

After the medicinal plants collection, they were properly set on blotting papers and old newspaper for absorbing moisture in order to avoid plants spoilage, attack of fungi and rotting. The newspapers were changed after every 24 hours. The plants were dried and made them moisture free by this process for twenty days. The plants were also sprayed with 2% mercuric chloride (HgCl<sub>2</sub>) as fungicides in order to prevent the fungal attack. The preservation process was completed in two months.

## Specimen identification

Preliminary confirmation of medicinal plants was made in the field using manuals, while unidentified samples were recognized using taxonomic keys, experts and herbarium materials at laboratory of plant taxonomy, Abdul Wali Khan University, Mardan Khyber Pakhtunkhwa, Pakistan.

## RESULTS AND DISCUSSION

The experimental and clinical information about botanicals suggest that district Swabi has diverse flora found in both hilly and plain areas (Fig. 2). In present study, four plants namely *Hordeum vulgare*, *Lantana camara*, *Melia azedarach* and *Rosa indica* had anticancer potentials along with other clinical uses. All the selected plants had multiple functions in the treatment of various diseases. The people of Swabi have been using these floras either as medicine or food, and hence these plants are known as central part of traditional pharmacopoeia. This study aimed to gather information on 24 Swabi medicinal plants with respect to ethnobotany, biochemistry and clinical uses (Table 1). The results showed the multiple uses of reported plants in the treatment of a lot number of diseases.

*Hordeum vulgare* is astringent, aphrodisiac, antilactagogue and stomachic. It is a natural remedy for catarrh and bronchitis. It is anti-cancer, anti-cholera and anti-cough. It is useful in the asthma and anemia ailments. It contains important compounds like  $\beta$ -glucan that is used against coronary heart diseases. The barley leaves have maximum amount of flavenoids and saponarin, and both of these compounds have strong antioxidant activities. It also contains an important essential element like magnesium, which serves as a co-factor for glucose metabolism and insulin level optimization (Lee et al., 2010; Kamiyama et al., 2012).

*Lantana camara* oil is antiseptic for wounds and is useful for leprosy and scabies. Various human ailments such as cancer, ulcers, asthma and eczema are effectively controlled by the plant extracts of *Lantana camara*. It is used in high blood pressure. It is anti-malaria, anti-bilious fevers, anti-tetanus. It is also used in tumors, catarrhal infections and rheumatism. *Melia azedarach* leaves are used for leprosy and antilithic. Its root is resolvent, and seeds are used as antirheumatism. It is used in sores and ulcers which don't have the tendency to heal. It is used for ringworm and scabies. The oil is insecticidal, antibacterial and used for malaria and leprosy. Alcoholic extract of stem bark is anticancerous, antispasmodic and antiviral. *Mentha longifolia* is antiseptic, beneficial in digestion. Its leaves and flowering stems have antiasthmatic and antidiarrhoeal properties. A tea from leaves is useful for fevers and headaches. *Mentha viridis* have expectorant, antiseptic, anti-bacterial potentials. It is used in headaches, rhinitis and sore throat. It is used in colic, cough and arthritis problems. It is also useful for alleviating swollen gums and mouth ulcers. It is anti-toothaches. The dry leaves are crushed, applied on the forehead in headaches. *Morus nigra* have analgesic, emollient, sedative, antibacterial properties and used in diabetes. The leaves are antibacterial, and used in colds and influenza. Eye infections and nosebleeds are treated with the dried leaves of *Morus nigra*. The stem is antirheumatic. Its fruit is laxative, nutritive and used in urinary incontinence, tinnitus and constipation in old age. Root bark is antitussive and used for asthmabronchitis and diabetes. *Nerium odorum* root and root-bark are powerful diuretic and cardiac tonic. *Nicotiana tabacum* is used for wound healing and headaches, curative for skin ailments, goiter, broken limes, headaches, ulcers, worms, syphilis and dropsy problems. Its various extracts are highly effective against gram positive and gram negative bacterial as well as many fungi species such as *Candida albican* and *Cryptococcus neoformans* (Maria et al., 2007).

*Opuntia dillenii* is used in burning sensations, hepatitis and asthma. It is also used for ulcers, edema and leucorrhoea. *Oxalis corniculata* is useful for dyspepsia, hemorrhoids, dysentery, diarrhea, dysmenorrhoea, amenorrhoea, hepatitis and burning sensation. The juice is used in stomach problems. The leaves are used as antiscorbic. *Phaseolus lunatus* seeds provide protein and carbohydrates rich diet and used as astringent,

diuretic. Seeds contain cuisine which eliminates blood cholesterol, osteoporosis. *Plantago ovate* husk of the seeds is taken as serbat for dysentery, laxative, reduces blood cholesterol levels and much valued for digestive ailments. *Prunus amygdalus* seeds are stimulant, demulcent and narvine tonic; useful in impotency, constipation and skin disorders. The oils are slightly laxative; in combination with amla juice very beneficial in hair loss and dandruff. *Psidium guajava* leaves are anticough and used in toothache, ulcers, inflamed gums and chest ailments. Roots are more effective for cholera patients. *Ricinus communis* oil is used as mild purgative, lubricant, hair tonic and to remove pain of bone's joints. If the oil is mixed with almond then it is useful for hair-restoration. Leaf decoction is useful in jaundice. *Rosa indica* is used for eye disorders, heart diseases, antifungal, anodyne, emmenagogue (flower) and anticancer (fruit). It is also used for stomach pains and swellings for the treatment of arthritis, boils and coughs.

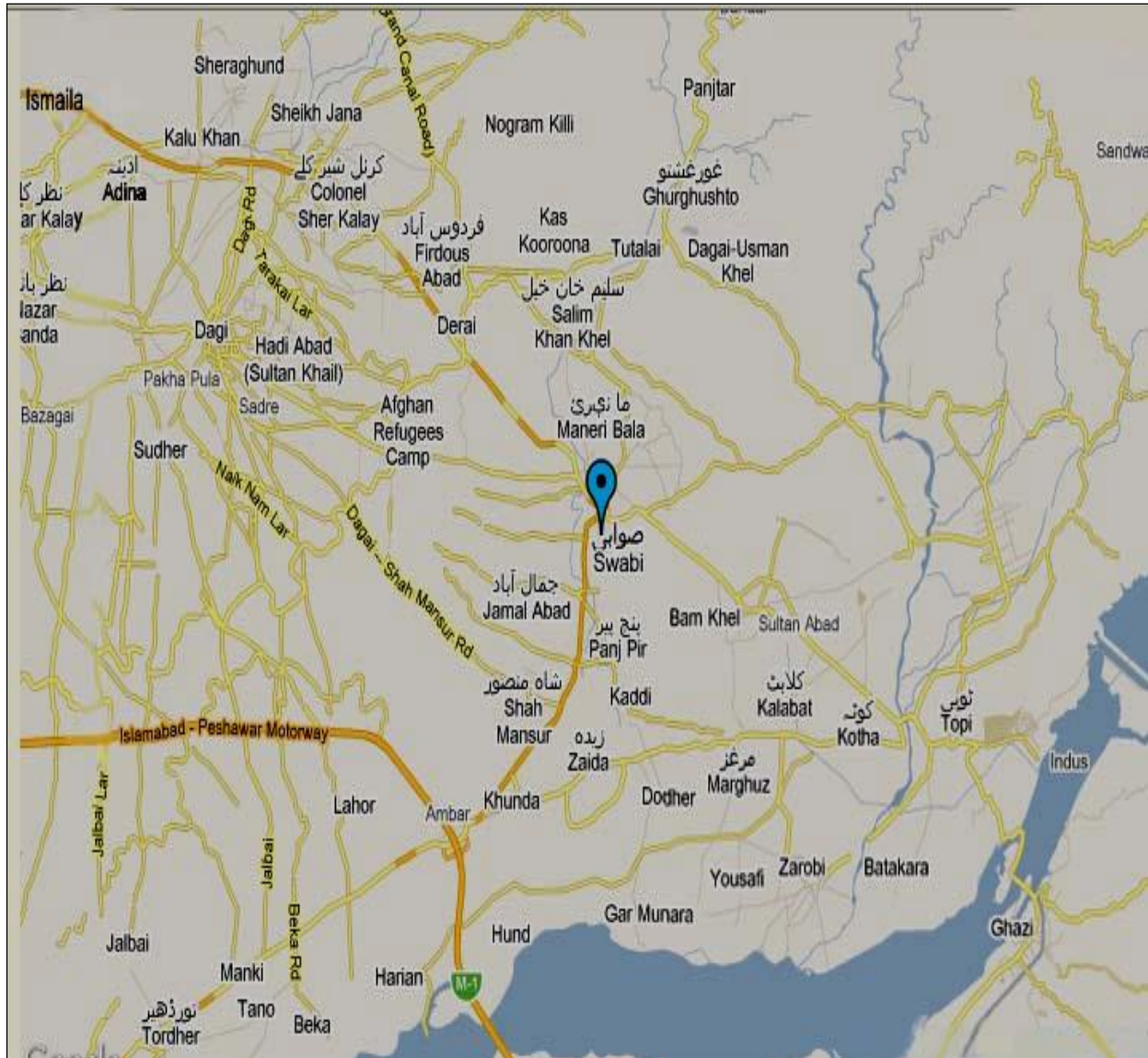


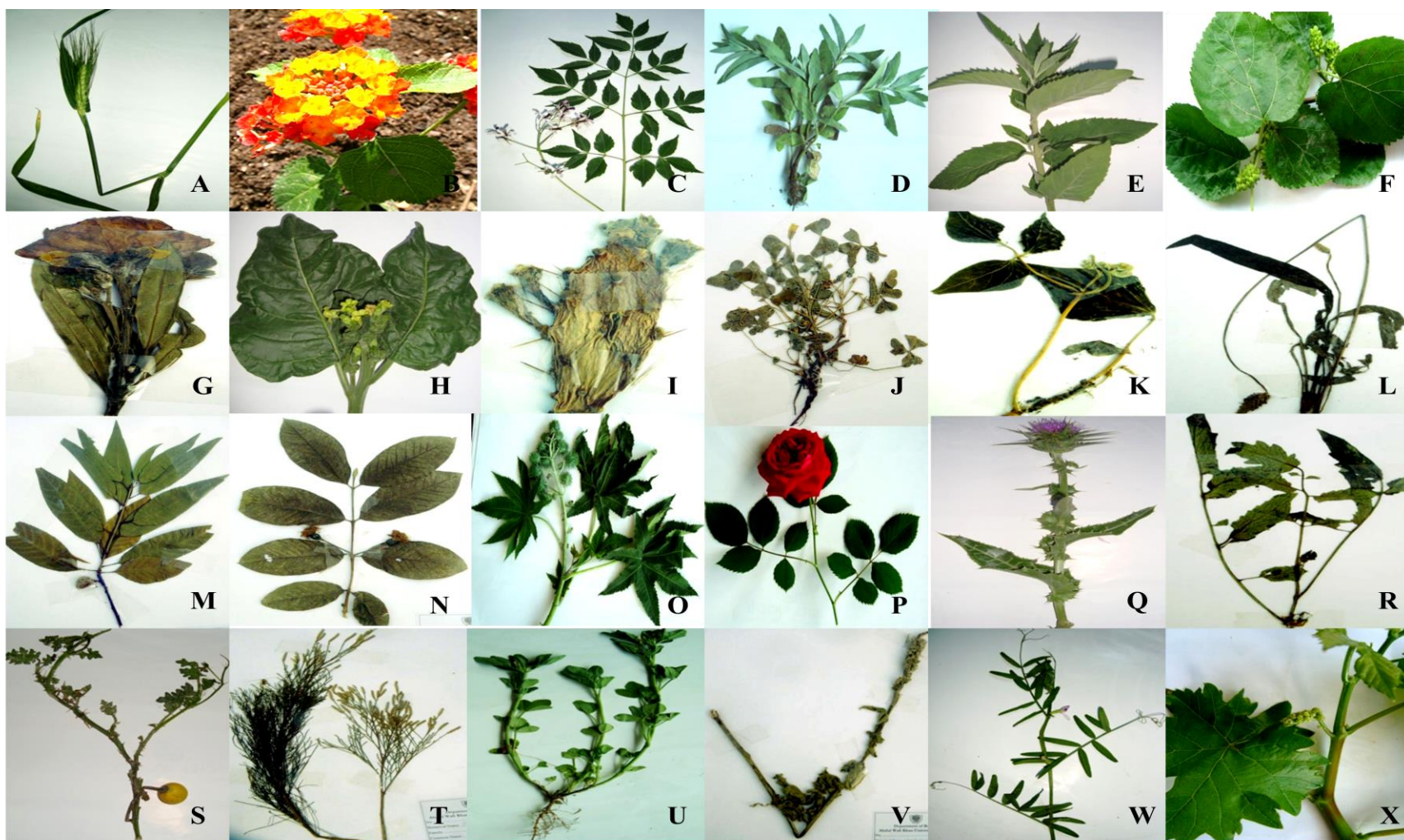
Fig. 1 Map showing study sites of hilly and plain areas of Swabi, Pakistan

**Table 1.** Taxonomic and phytochemical study of medicinal plants collected from hilly and plain areas of Swabi, Pakistan

Botanical name	Local name	Phytochemicals	Medicinal uses
<i>Hordeum vulgare</i>	Jao	Protein, Fat, Carbohydrate, Fiber, Ash, Thiamine, Riboflavin, Niacin, Arginine, Histidine, Lysine, Tyrosine, Tryptophane, Phenylalanine, Cystine, Methionine, Threonine, Leucine	For Bronchitis, Burns, Cancer, Catarrh, Chest, Chilblains, Cholecystosis, Cholera, Cough, Debility, Diarrhea, Dyspepsia, Fever, Inflammation, Measles
<i>Lantana camara</i>	Panch phul	Pentacyclic Riterpenoids, Lantoside, Lantanone, Lancamaric acid, Ursangilic acid, Oleanolic acid, Acetate, Tetracosanoic acid, Octadecanoic acid, Palmitic acid, Oleanolic acid, Oleanonic acid	Plant extracts are used treatment of Chicken pox, Measles, Swellings, Eczema, Tumors, High blood pressure, Bilious fevers, Catarrhal infections, Tetanus, Rheumatism, Malaria
<i>Melia azedarach</i>	Bakain	Bakayanin, Rutin, Quercitrin, Backalactone, Cystine, Serine, Arginine, Glycine, Glutamic acid, Proline	Leaves, root, seed: For Leprosy, Scrofula, Anthelmintic, Antilithic, Diuretic, Deobstruent, Resolvent, Sores, Ulcers, Ringworm, Scabies, Malaria fever
<i>Mentha longifolia</i>	Velane	Volatile oil, Thymole, Resine, Tannin, Gum, Pulegone, Isomenthone, Borneol, Piperitenone oxide	Leaves, flowering stem: Antiasthmatic, Antispasmodic, Antidiarrhoeal, Carminative, Fevers, Headaches, Digestive disorders
<i>Mentha viridis</i>	Podina	Volatile oil, Carvone, Limonene, Trans-carveol, Linarin, Pulegone, Menthol, Menthene, Menthenone, Phellandrine, Limonene, Dihydrocarveol acetate	Leaves: Carminative, Expectorant, Antiseptic, Anti-bacterial, Headaches, Rhinitis, Cough, Sore throat, Colic, Prurigo, Arthritis, Vomiting, Fever
<i>Morus nigra</i>	Tooth siah	Hallucinogens, Hydroxyresveratrol, Dihydromorin, Morin, Sanggenol, $\beta$ -sitosterol	Leaves, stem, fruit, root bark: For Diabetes. Colds, Influenza, Eye infections
<i>Nerium odorum</i>	Gandere	Glucoside, Rosaginine, Tannic acid, Wax	Root, Root-bark: powerful diuretic and cardiac tonic
<i>Nicotiana tabaccum</i>	Tamakoo	Nicotine, Nicotianin, Nicotinine, Nicoteine, Nicoteline, Cholin, Anabesine, Nabasine	Leaves: For wound healing and headaches, curative for skin ailments, sedative, diuretic, expectorant, discutient, sialagogue, internally only as an emetic, goiter
<i>Opuntia dillenii</i>	Zukam	Opuntiol, Ferulic acid, Hydroxybenzoic acid, Malic acid, 3-O-methyl isorhamnein, 1-Heptanecanol, Vanillic acid, Isorhamnetin-3-O-beta-D-rutinoside	For burning sensations, Whooping cough, Hepatitis, Asthma, Poison, Fever, Constipation, Conjunctivitis, Edema, Leucorrhoea, Menorrhagia
<i>Oxalis corniculata</i>	Khatibuti	Oxalic acid, Tannins, Potassium, Palmitic acid, Vitamin C	Leaves, Juice of plant: Used for Dyspepsia, Hemorrhoids, Dysentery, Diarrhea
<i>Phaseolus lunatus</i>	Lobyas	Phaseolunatin Cuisinine, Carbohydrate, Protein, Lectin, Phytin, Tannin, Linamarin, Glucoside, Folic acid, Manganese, Vitamin B	Leaves, stems, seeds: Used as astringent, diuretic, seeds contain cuisine which eliminate blood cholesterol, while manganese prevent osteoporosis
<i>Plantago ovate</i>	Espaghol	Protein, Mucilage, Fiber, Albumin, Globulin, Prolamin, Linoleic acid, Oleic acid, Xylose, Arabinose, Galaecturonic acid, Rhanose, Galactose, Albumin, Tannin, Acetylcholine	<i>Plantago ovate</i> husk of the seeds taken as serbat for dysentery, Laxative, reduces blood cholesterol levels and much valued for digestive ailments
<i>Prunus amygdalus</i>	Badam	Fixed oil, Mucilage, Sugar, Iron, Phosphorus, Calcium, Niacin, Sphingolipid, $\beta$ -d-glucopyranosyl, $\beta$ -sitosterol, Daucosterol, Uridine,	Seeds, Oil: Stimulant, Demulcent, Narvine tonic, useful in impotency, constipation and also use for skin disorders. The

		Adenosine	oils are slightly laxative
<i>Psidium guajava</i>	Amrood	Ascorbic acid, Iron, Pentacyclic, Triterpenoid, Guajanoic acid, $\beta$ -sitosterol, Uvaol, Oleanolic acid, Ursolic acid	Roots, Bark, Leaves, Immature fruits: To halt gastroenteritis, Diarrhea, Dysentery
<i>Ricinus communis</i>	Arand	Alkaloid ricinine, Toxalbumin, Lipids, Fixed oil, Triricinolin	Oil used as mild purgative, lubricant and hair tonic
<i>Rosa indica</i>	Surkh gulab	Fresh flowers of <i>Rosa indica</i> yields 0.013 to 0.15% essential oil. Composition of this essential oil is 22.1% stearoptenas, 16.36% phenethyl alcohol, 12.78% geraniol, 23.39% citronellol and gallic acid	Fresh flowers: Used for eye disorders, heart diseases, antifungal, anodyne, emmenagogue, anticancer, stomach pains and swellings for the treatment of arthritis, boils and coughs
<i>Silybum marianum</i>	Kariza	Flavone Lignans, Linoleic acid, Oleic acid, Palmitic acid, Protein, Stigmasterol, Sitosterol;	It is used in cirrhosis, jaundice and hepatitis ailments.
<i>Solanum nigrum</i>	Kachmac hoo	Alkaloid, Solanine, Solanidine, Saponin, Alpha, Beta Gamma Chaconines, Alpha, Beta Gamma Solanines	It is used in spleen enlargement, and root acts as a useful drug in hepatitis C. It is a good anti rheumatism drug.
<i>Solanum xanthocarpum</i>	Maraghu ne	Steroidal alkaloid; Solasodine, Glycoalkaloid, Diosgenin, Alcoholic extracts. Fruit contains Solasonine, Sterols, Carpesterol	Its root is used for catarrh, asthma and bronchospasm, while fruit and root are good drug for flatulence and toothache
<i>Tamarix gallica</i>	Ghazz	Akaloid, Tamarixin, Aglocone, Tamarixetin.	<i>Tamarix gallica</i> is used in healing of wounds.
<i>Trigonella foenum-graecum</i>	Malhuz	Mucilage, Calcium, Phosphorus, Iron. Protoalkaloids, Trigonelline, Choline, Saponins	It is used in digestive and menstrual pains. It increases breast milk. It is used to reduce cholesterol level in blood and sugar in urine.
<i>Verbascum Thapsus</i>		Volatile oil, Saponin, Amaroid, Gum, Mucilage, Resins	It is an expectorant, as well as an anodyne. Its leaves and flowers are used in hay fever. It is used in respiratory, coughs and colds problems.
<i>Vicia sativa</i>	Chelu	Volatile oil, Protein, Ash, Fiber, Aliphatic hydrocarbons, Aldehydes, Ketones	<i>Vicia sativa</i> seed is useful for emollient.
<i>Vitis vinifera</i>	Angoor	Oxalic acid, Malic acid, Tartaric acid, Linoleic acid, Oleic acid, Palmitic acid, Stearic acid, Palmitoleic acid, Phenols, Tocopherols, Steroids, Campesterol, Beta-sitosterol, Stigmasterol, Vitamin E	It is used as astringent, while fruit has cooling, stomachic and laxative properties. Fruit is also used in cardiac pain and heart palpitation and acts as an excellent source of blood builder





**Fig. 2 Identification and collection of 24 selected medicinal plants from hilly and plain areas of Swabi** (A) *Hordeum vulgare* (B) *Lantana camara* (C) *Melia azedarach* (D) *Mentha longifolia* (E) *Mentha viridis* (F) *Morus nigra* (G) *Nerium odorum* (H) *Nicotiana tabacum* (I) *Opuntia dillenii* (J) *Oxalis corniculata* (K) *Phaseolus lunatus* (L) *Plantago ovata* (M) *Prunus amygdalus* (N) *Psidium guajava* (O) *Ricinus communis* (P) *Rosa indica* (Q) *Silybum marianum* (R) *Solanum nigrum* (S) *Solanum xanthocarpum* (T) *Tamarix gallica* (U) *Trigonella foenum-graecum* (V) *Verbascum thapsus* (W) *Vicia sativa* (X) *Vitis vinifera*

*Silybum marianum* is used in cirrhosis, jaundice and hepatitis ailments. *Solanum nigrum* is used in spleen enlargement, and root acts as a useful drug in hepatitis C. It is a good anti rheumatism drug. *Solanum xanthocarpum*'s root is used for catarrh, asthma and bronchospasm, while fruit and root are good drug for flatulence and toothache. Fruit are also useful for anthelmintic and indigestion. *Tamarix gallica* is antifouls, antiulcers and antidiarrhoea. It is also used in healing of wounds. *Trigonella foenum-graecum* is used in digestive and menstrual pains. It increases breast milk. It is used to reduce cholesterol level in blood and sugar in urine. Seeds are used in aphrodisiacs.

*Verbascum thapsus* is an expectorant as well as an anodyne. Its leaves and flowers are used in hay fever. It is used in respiratory, coughs and colds problems. It is antiemphysema and effective in asthma. The roots are boiled and used in bladder incontinence. Oil is used for ear infections, hemorrhoids and bronchial inflammation. Oil is also used as an effective drug for chest congestion, swollen joints and arthritis. *Vicia sativa* seed is useful for emollient. *Vitis vinifera* is used as astringent, while fruit has cooling, stomachic and laxative properties. Fruit is also used in cardiac pain and heart palpitation and acts as an excellent source of blood builder.

A similar type of research study was carried out by investigating the effects of Chinese medicinal plants in China for the treatment of various human ailments. It has been documented in this study that previous research notes and ethnobotanical surveys reported plant remedies for the treatment of diabetes and concluded that these ancient Chinese medical articles and ethnobotanical surveys provided a base line for drug discovery to alleviate epidemic diabetes at global level (Ma et al., 2014). Similarly, Hussain et al. (2013) conducted a detailed study about medicinal plants of Parachinar (FATA) Khyber Pakhtunkhwa, Pakistan based on folk knowledge to motivate the local people of Parachinar to use botanicals in an efficient manner. In their study, it was reported that area had high diversity as well as precious medicinal plants that have been used traditionally to treat various human ailments. Kidane et al. (2014) investigated the use of botanicals in Southern Ethiopia for the treatment of human health issues and reported that about 80% of inhabitants of Ethiopia relied on medicinal plants for curing various diseases. In their study, qualitative and quantitative field survey, and individual and group discussions were followed to generate scientific data about testing to verify the efficacy and dosage of medicinal plants to alleviate major threats to human health. Abera (2014) scrutinized the effects of medicinal plants of district Ghimbi, Southwest Ethiopia and documented that ethnobotany is a real and rich biological source for the identification, certification, status and proper usage of medicinal plants. This research group collected information about medicinal plants by field observation and interviewing 30 key informants and 165 local members and ascertained that 49 botanicals were used to treat various human diseases in Ethiopia.

The same nature of research study was conducted in district Swat, Pakistan in which local farmers, collectors and dealers were interviewed about the collection efforts, number of botanicals collected, price obtained and their net income from medicinal plants. From this research survey, it was noticed that collection of wild plants was only source of botanicals raw material for human ailments, with actually no cultivation. It was inferred that medicinal plants had great economic benefits but there were some drawbacks in market which could be addressed by proper knowledge of medicinal plants, efficient linkages in market chain and appropriate harvesting practices (Sher et al., 2014).

## CONCLUSION

This study aimed to collect the wild sources of medicinal plants in Swabi, Pakistan. The results of this study corroborated the large population of medicinal plants that were more effective against various human ailments. The present data could be a significant part of both pharmaceutical industries of Pakistan and local farms that specialized in medicinal plants cultivation. These botanicals possessing medicinal properties might provide a basic raw material for making huge medicinal preparations. This raw material of botanicals should be produced at standard quality that would allow us to estimate and control these plants during cultivation and selection.



**Author Contribution Statement** Muhammad Qasim conducted the research study. Muhammad Khalid and Aqib Sayyed helped in survey and collecting information. Ismail din contributed in plants collection and preservation. Kashif Hayat analyzed the data. Sohail Ahmad Jan wrote the manuscript. Rozina edited the manuscript. All the authors have read and approved the manuscript.

**Conflict of Interest** The authors declare that they have no conflict of interest.

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