One of the major diseases that affect human population since ancient ages are the kidney stones (renal calculi). Kidney stones result in the modification of the victim’s behavior with great fear of intense pain and threaten with failure of the kidneys. Urinary stones contain both crystalloid and colloid components. The crystalloid components are mainly calcium oxalate, calcium phosphate, calcium carbonate, magnesium-ammonium phosphate, uric acid and cysteine. Various drugs are available for the treatment of this disease. Moreover, advancements in medical techniques have led to the development of invasive methods of stone disruption like lithotripsy and surgical methods. But these are very expensive methods which are non-affordable by the poor people and the rate of reoccurrence is also high from 50 to 80% (1). The remedy that is the safest and cheapest includes the use of medicinal plants. Medicinal plants have occupied an important place in the society of developing countries, not only as a source of economy but also for improving quality of life, because 80% of human population prefer using herbal remedies (2).

Modern pharmacopoeia includes at least 25% of the drugs coming from plant origin, 121 of such active substances are being in use currently or synthetic analogs are obtained from natural precursors. Hence, potential of medicinal plants cannot be underestimated (3). Various plants have been reported to be used for the treatment of kidney stones.
However, to the best of our knowledge and according to the literature survey, a majority of the medicinal plants of Pakistan have not been scientifically evaluated for their potential in the treatment of kidney stones.

In this article, 35 medicinal plants of Pakistan origin and their crucial information have been enumerated in alphabetical order of plant’s scientific name, family, place (distribution), part used, local name, habit, major constituents and references.

**METHODOLOGY**

Data collection was carried out through internet search on Science Direct, Google and PubMed using biological and chemical abstracts. The key words used for the literature survey for this article were “Medicinal plants of Pakistan, kidney stones, renal calculi, ethnobotanical evidence and natural products”. Selection of plants was focused on their use in the treatment of kidney stones in folklore remedies and studied their references in detail. Chemical constituent of medicinal plants were also searched. The outcome of results were rechecked and compared with the literature.

**RESULTS AND DISCUSSION**

Urolithiasis is a major problem afflicting human civilization for several centuries. It has been observed that its annual incidence is 0.5% in western world. The major phenomenon responsible for stone formation involves calcium oxalate and calcium phosphate accumulation. The phases involved in the accumulation of these two substances include: nucleation, crystal growth, crystal aggregation and crystal retention (55). Nucleation phase involves the formation of a solid crystal. It is the primary step in the formation of renal stone. The underlying cause for nucleation is super-saturation. The homogeneous nucleation involves the nucleation in pure solution, whereas secondary nucleation involves the accumulation of new crystals on pre-existing crystals. Urine is not a pure substance and nucleation in it involves the presence of an existing surface or structure. This phenomenon is called heterogeneous nucleation (58). Heterogeneous nucleation in urine may occur at epithelial cells, RBCs, bacteria, some other crystals, cell debris and urinary casts. Stone formation involves phase change which results in the condensation of dissolved solids transforming these into solid state because of super-saturation. Nucleation is followed by the crystal growth. The crystal growth process begins with the nucleation stage. Super-saturation facilitates the process of cluster formation. In the 3rd phase (crystal aggregation/crystal agglomeration), the crystals stick together and constitute a larger particle. Stabilization is achieved by the bridge formation among the crystalline substance (24). Finally, these crystals are retained in the kidney. The retention is achieved because of adherence of crystals with epithelial cell line (41).

Stone formation inhibitors forbid the agglomeration and growth by developing a layer on the surface of growing calcium crystals or by forming complexes with calcium and oxalate. There are various substances that inhibit the stone formation including both organic and inorganic substances. Inorganic substances include citrates, magnesium and pyrophosphates while organic substances include Tamm-Horsfall proteins, urinary prothrombin fragment 1, protease inhibitor (inter-α-inhibitor), glycosaminoglycans, osteopontin (uropontin), renal lectin and others like bikunin and calgranulin. High urine flow is also an important inhibitor of kidney stone formation (55).

Phytochemical investigation for use as urolithic agent is still an era of thirst. Only a few phytochemicals have been investigated to have a role in urolithiasis. Some terpenoids have been reported to have this activity (56, 57). Some flavonoids like quercetin, kaempferol-3-rhamnogalactoside and kaempferol-3-rhamnoside and tannins have also been reported to have some effect (60).

Plant extracts may contain chemicals and phytochemicals that inhibit the synthesis and growth of crystals. This character of plants may be of significant importance in preventing kidney stone formation. The extracts of plants may also contain constituents that retard crystal agglomeration (58).

The history of use of herbal remedies starts from the very beginning of human civilization. Various plants have been reported to be used in the treatment of disorders, but the knowledge of treatment differ in various areas and it is just like a hidden treasure. The present study is an effort to bring out the hidden treasure of knowledge used in the treatment of kidney stones in Pakistan. In this article, 35 medicinal plants of Pakistan and their crucial information have been enumerated in alphabetical order of plant scientific name, family, place (distribution), part used, local name, habit, major constituents and references (Table 1). These plants are distributed in 21 families of which, Cucurbitaceae represents the maximum contribution with 4 plants. Asteraceae, Fabaceae and Solanaceae are the families contributing 3 plants. Amaranthaceae, Boraginaceae, Chenopodiaceae, Rosaceae and Rutaceae are
Table 1. Medicinal plants of Pakistan used for the treatment in kidney stone.

<table>
<thead>
<tr>
<th>Scientific Name</th>
<th>Family</th>
<th>Location</th>
<th>Constituents active against urolithiasis</th>
<th>Habit</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Acacia Jacquemontii</em> Benth.</td>
<td>Fabaceae</td>
<td>Sindh****, Punjab*, Baluchistan**</td>
<td>Diterpenoids</td>
<td>Terpenoids</td>
<td>4, 56</td>
</tr>
<tr>
<td><em>Achillea millefolium</em> L.</td>
<td>Asteraceae</td>
<td>Himalayan Region and Azad Kashmir*</td>
<td>Saponins, essential oils, flavonoids</td>
<td>Flavonoids</td>
<td>5, 6, 60, 63</td>
</tr>
<tr>
<td><em>Achyranthus aspera</em> L.</td>
<td>Amaranthaceae</td>
<td>Swat, Bhamber, Azad Jammu and Kashmir*</td>
<td>Saponins, oleanolic acid, flavonoids, dihydroxyketones, alkaloids</td>
<td>Flavonoids</td>
<td>7, 8, 60, 64-66</td>
</tr>
<tr>
<td><em>Aerva javanica</em> (Burm. f.) Schult.</td>
<td>Amaranthaceae</td>
<td>Parachinar, Kurram Agency, Kohat***</td>
<td>Alkaloids, flavonoids, tannins</td>
<td>Herb</td>
<td>9-14, 60</td>
</tr>
<tr>
<td><em>Asphodelus tenuifolius</em> Cavan.</td>
<td>Liliaceae</td>
<td>Bhamber****</td>
<td>β-Sitosterol, 1-octacosanol, 1-triacontanol, hexadecanoic acid, tetracosanoic acid, triacontanolic acid, 3-hydroxybenzoic acid and β-sitosterol 3-O-β-D-glucopyranoside</td>
<td>Not yet identified</td>
<td>Herb</td>
</tr>
<tr>
<td><em>Bergenia ciliate</em> (Haw.) Stemmb.</td>
<td>Saxifragaceae</td>
<td>Azad Kashmir*****</td>
<td>Wax, gallic acid, tannin, bergenin, mucilage</td>
<td>Tannin</td>
<td>Herb</td>
</tr>
<tr>
<td><em>Bryophyllum pinnatum</em> (Lam.) Oken</td>
<td>Crassulaceae</td>
<td>Bhamber****</td>
<td>Alkaloids, triterpenes, glycosides, flavonoids, steroids, bufadienolides, lipids and organic acids.</td>
<td>Terpenoids, flavonoids</td>
<td>Herb</td>
</tr>
<tr>
<td><em>Calendula officinalis</em> L.</td>
<td>Asteraceae</td>
<td>Pooch valley****</td>
<td>Triterpenoids, flavonoids, coumarins, quinones, volatile oil, carotenoids and amino acids</td>
<td>Terpenoids, flavonoids</td>
<td>Herb</td>
</tr>
<tr>
<td><em>Chenopodium album</em> L.</td>
<td>Chenopodiaceae</td>
<td>Tank***</td>
<td>Oxalic acid, essential oil, vitamin A and C, alkaloid, flavonoid</td>
<td>Flavonoid</td>
<td>Weed</td>
</tr>
<tr>
<td><em>Cichorium intybus</em> L.</td>
<td>Asteraceae</td>
<td>Swat****</td>
<td>Inulin, esculin, volatile compounds (monoterpenes and sesquiterpenes), coumarins, flavonoids and vitamins</td>
<td>Flavonoids</td>
<td>Herb</td>
</tr>
<tr>
<td><em>Citrullus colocynthis</em> (L.) Schrad.</td>
<td>Cucurbitaceae</td>
<td>Dadu****</td>
<td>Alkaloids, anthraquinones, flavonoids, terpenes, tannins, steroids, cardiac glycosides and saponins</td>
<td>Terpenoids, flavonoids, tannins</td>
<td>Herb</td>
</tr>
<tr>
<td><em>Citrullus vulgaris</em> Schrad. ex Eckl. and Zeyh.</td>
<td>Cucurbitaceae</td>
<td>Tehsil Pindigheh, District Attock*</td>
<td>Tannin, phytate, oxalate, iron, calcium, zinc</td>
<td>Tannins</td>
<td>Herb</td>
</tr>
<tr>
<td><em>Citrus sinensis</em> (L.) Osbeck, Reise Ostind</td>
<td>Rutaceae</td>
<td>Sindh****</td>
<td>Reducing sugar, saponins, cardiac glycosides, tannins and flavonoids</td>
<td>Flavonoids, tannins</td>
<td>Tree</td>
</tr>
<tr>
<td>Scientific Name</td>
<td>Family</td>
<td>Location</td>
<td>Constituent(s) against urolithiasis</td>
<td>Constituents active against urolithiasis</td>
<td>Habit</td>
</tr>
<tr>
<td>-----------------</td>
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<td>----------------------------------</td>
<td>----------------------------------------</td>
<td>-------</td>
</tr>
<tr>
<td><em>Citrus aurantifolia</em> (L.)</td>
<td>Rutaceae</td>
<td>Sindh</td>
<td>Polymethoxyflavones (PMFs), (Christman) Swingle</td>
<td>Polymethoxylated flavones, Flavonoids, O-glycosylated flavones</td>
<td>Tree</td>
</tr>
<tr>
<td><em>Cucumis melo</em> L.</td>
<td>Cucurbitaceae</td>
<td>Nara Desert, Sindh</td>
<td>Alkaloids, triterpenoids, carbohydrates, proteins, flavonoids, phytosterols</td>
<td>Terpenoids, flavonoids</td>
<td>Shrub</td>
</tr>
<tr>
<td><em>Cucumis sativus</em> L.</td>
<td>Cucurbitaceae</td>
<td>Kohat</td>
<td>Alkaloids, glycosides, steroids, tannins</td>
<td>Tannins</td>
<td>Herb</td>
</tr>
<tr>
<td><em>Dolichos biflorus</em> L.</td>
<td>Fabaceae</td>
<td>Sindh</td>
<td>Falconoid phenolicNot yet identified</td>
<td>Not yet identified</td>
<td>Herb</td>
</tr>
<tr>
<td><em>Ficus carica</em> L.</td>
<td>Moraceae</td>
<td>Chagharzai Valley</td>
<td>Flavonoid, alkaloid, tannin, saponin</td>
<td>Flavonoids, tannins</td>
<td>Tree</td>
</tr>
<tr>
<td><em>Haloxylon stocksii</em> (Boiss.)</td>
<td>Chenopodiaceae</td>
<td>Coastal of Karachi</td>
<td>Dillenic acid</td>
<td>Not yet identified</td>
<td>Shrubs</td>
</tr>
<tr>
<td><em>Heliotropium strigosum</em> Willd.</td>
<td>Boraginaceae</td>
<td>Bhimber</td>
<td>Flavonoids, essential oil</td>
<td>Essential oils</td>
<td>Wild herb</td>
</tr>
<tr>
<td><em>Micromeria biflora</em> (Buch.-Ham. ex D. Don)</td>
<td>Labiatae</td>
<td>Pooch valley</td>
<td>Essential oils</td>
<td>Not yet identified</td>
<td>Herb</td>
</tr>
<tr>
<td><em>Nigella sativa</em> L.</td>
<td>Ranunculaceae</td>
<td>Faisalabad, Hasilpur, Lahore, Multan</td>
<td>Alkaloids, tannins, flavonoids</td>
<td>Flavonoids, tannins</td>
<td>Herb</td>
</tr>
<tr>
<td><em>Rubus ellipticus</em> Smith.</td>
<td>Rosaceae</td>
<td>Swat</td>
<td>steroids, tannins and phenolic compounds, terpenoids, alkaloids</td>
<td>Flavonoids, carbohydrates, sterols, tannins</td>
<td>Shrub</td>
</tr>
<tr>
<td><em>Senna italica</em></td>
<td>Fabaceae</td>
<td>Sindh</td>
<td>1,5-dihydroxy-3-methylanthraquinone, anthraquinone, alkaloids, steroids, flavonoids, tannins, proteins</td>
<td>Flavonoids, polynuclear aromatics, alkaloids</td>
<td>Shrub</td>
</tr>
<tr>
<td><em>Solanum nigrum</em> L.</td>
<td>Solanaceae</td>
<td>Upper Dir</td>
<td>Alkaloids, pregnane saponins, solanigroside A, tannins, flavonoids, proteins</td>
<td>Flavonoids, tannins</td>
<td>Herb</td>
</tr>
</tbody>
</table>

Table 1. cont.
<table>
<thead>
<tr>
<th>Scientific Name</th>
<th>Family</th>
<th>Location</th>
<th>Constituent</th>
<th>Constituents active against urolithiasis</th>
<th>Habit</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Solanum surattense</em> Shord and Wendl</td>
<td>Solanaceae</td>
<td>Poonch valley****</td>
<td>Oil, alkaloids, potassium nitrate, carbohydrates, tannins phenols, gums and mucilages</td>
<td>Tannins</td>
<td>Herb</td>
<td>5, 17, 60, 69</td>
</tr>
<tr>
<td><em>Tamarix aphylla</em> (L.) Karst.</td>
<td>Tamaricaceae</td>
<td>Sindh******</td>
<td>Glycosylated isoferric acid, tamarixetin 3,3’-disodium sulfate, dehydrodigallic acid dimethyl ester and isoferric acid, ferulic acid, kaempferol 7,4’-dimethyl-ether-3-sulfate, quercetin 3-O-isoferril-β-glucuronide, alkaloids, flavonoids, tannins</td>
<td>Flavonoids, tannins</td>
<td>Trees shrub</td>
<td>4, 60, 70</td>
</tr>
<tr>
<td><em>Trianthema potulacastrum</em> L.</td>
<td>Aizoaceae</td>
<td>Bhimber***</td>
<td>Tetraterpenoid 1 (trianthenol), flavonoid, (C-methyl flavone), alkaloid (trianthemine)</td>
<td>Terpenoids</td>
<td>Herb</td>
<td>15, 49, 56</td>
</tr>
<tr>
<td><em>Tribulus terrestris</em> L.</td>
<td>Zygophyllaceae</td>
<td>Bhimber****</td>
<td>Saponins, diosgenins, alkaloids, amides, tannins, flavonoids</td>
<td>Flavonoids, tannins</td>
<td>Herb</td>
<td>15, 50, 60, 71</td>
</tr>
<tr>
<td><em>Trichodesma indicum</em> (L.) R. Br.</td>
<td>Boraginaceae</td>
<td>Poonch valley****</td>
<td>Fatty acids and non-steroidal compounds.</td>
<td>Not yet identified</td>
<td>Herb</td>
<td>5, 17, 51</td>
</tr>
<tr>
<td><em>Vitex agnus-castus</em> L.</td>
<td>Verbenaceae</td>
<td>Khuzdar, Wadh**</td>
<td>Iridoids, flavonoids, diterpenoids, essential oils, ketosteroids</td>
<td>Terpenoids, flavonoids</td>
<td>Shrub</td>
<td>52, 53, 56</td>
</tr>
<tr>
<td><em>Withania somnifera</em> (L.) Dunal</td>
<td>Solanaceae</td>
<td>Khushab, Cholistan desert*</td>
<td>Withanolides, cytotoxic lactones, piperidine, anaferine, anhydrogyne, alkaloids (withanine, somniferine, sommine, tropine, triterpenes)</td>
<td>Terpenoids</td>
<td>Herb</td>
<td>43, 44, 54, 56, 72</td>
</tr>
<tr>
<td><em>Zea mays</em> L.</td>
<td>Poaceae</td>
<td>Sindh****</td>
<td>Flavonoids, alkaloids, phenols, steroids, glycosides, carbohydrates, amino acids, terpenoids, tannins</td>
<td>Flavonoids, tannins</td>
<td>Bushes</td>
<td>4, 56, 60, 61</td>
</tr>
</tbody>
</table>

*East of Pakistan, **West of Pakistan, ***North of Pakistan, ****North-west of Pakistan, *****South of Pakistan
the families contributing 2 species, while, Aizoaceae, Crassulaceae, Labiatae, Liliaceae, Moraceae, Poaceae, Polygalaceae, Ranunculaceae, Saxifragaceae, Tamaricaceae, Verbenaceae and Zygophyllaceae, were found with single medicinal plant of such potential (Fig. 1). These plants are distributed throughout Pakistan in all the provinces. It can also be seen that all parts are used for the treatment of kidney stones. Leaves represent 28% contribution, whole plants and seeds 12%, fruit and roots 11% contribution in this respect. Flowers contribute 8% in the treatment of kidney stone while branches, bark, bushes, buds, milk and shoots contribute only 3% in the removal of kidney stones (Fig. 2). Habits of plants were also taken under consideration. It was noticed that herbs are the most useful life form in this regard which contributed 63% for the removal of kidney stones. Shrubs contributed 20%, trees 11% while bushes and weeds contributed 3% for the removal of kidney stones (Fig. 3).

During ethnobotanical search of Pakistan 35 medicinal plants belonging to 21 families were recorded as effective remedies used by the local people for the removal of renal calculi (kidney stones). These crude drugs cause dissolution or breakage of the renal calculi with subsequent expulsion from the body. The phenomenon of dissolution or destruction may be caused by the phytochemicals present in the crude drugs so plants were also searched for chemicals.

CONCLUSION

The present article enlists 35 medicinal plants used by the local people for the treatment and removal of renal calculi in various areas of Pakistan.
Pakistan. The medicinal plants used for the treatment of renal calculi contain such constituents which are active against urolithiasis. These active constituents include flavonoids, terpenoids, and tannins. Chemical investigation of medicinal plants is another important thirsting era that may lead to the understanding of physiology, pathology and pharmacology and use of these plants for various other diseases.

REFERENCES