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REVEND (RHUBARB): AN IMPORTANT UNANI DRUG FOR PREVENTION OF NEPHROTOXICITY

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ABSTRACT: Rheum emodi commonly known as Rhubarb belongs to family Polygonaceae is called as Revand in Unani System of Medicine. The drug is usually regarded as Rhubarb. Traditionally plant is widely used as tonic, diuretic, laxative, and to treat ulcers, diarrhea, fever, cough and indigestion. Aim of this paper is to review the role of Rheum in prevention of Nephrotoxicity. Rhubarb material related to its nephroprotective activity was collected from journals, pharmacopeia, books and classical literature of Unani Scholars. Ibn-e-Sina (978-1023 AD) described both the plant "Ribas" (Riwas, Persian) and the drug "Rewand" (Rawand, Persian). "Mesue" (Masih), early in the 11th century, distinguished between Chinese and Khorasan Rhubarb (Dymock et al 1890, Engelshowe 1985, Butler and Moffett 1995). "Haji Zein-al-Attar" (1368 Hijri) considered "Rewand" to be the same as "Ribas". According to "Ibn-e-Jazla", there are two kinds of Rhubarb, China and Khorasan Rhubarb, and that the later is known as `Rewand-aldawaab', and is used in veterinary practice, whilst the Chinese is reserved for human beings. On the basis of researches carried out on Rheum it is evident that it has a potential to prevent the nephrotoxicity. It is also useful in the treatment diseases like cancer, microbial, inflammation, and fungal infections, liver, diabetes, and kidney disease. The plant is found high potent antioxidant activity. These studies raised the therapeutic efficacy of rhubarb. This review covers all the detail study of rhubarb plant with special reference to the nephroprotective function.

INTRODUCTION:

Revand (Rhubarb) is the dried rhizomes of the species of Rheum (Polygonaceae). The Chinese appear to have been acquainted with the properties of Rhubarb so called "Pen-king" from a period long anterior to the Christian era. It was attributed to the Emperor "Shen-nung" the father of Chinese agriculture and medicine, who reigned about 2700 B.C. The drug is named there "Huang-Hang" (means yellow, excellent) and "Ta-huang" (means the great yellow). The later name was retained for 2000 years by the traders who collected it in Tibet and the province of Kansu.

As regards Western Asia and Europe, we find a root called `Rha' or `Rheon' mentioned by "Dioscorides" as brought from beyond the Bosphorus. "Pliny" describes a root termed `Rhacoma' which, when pounded, yielded a colour like that of wine, but inclining to saffron, and was brought from beyond "Pontus". The drug thus described is usually regarded as Rhubarb, or at least as the root of some species of Rheum. "Lassen" has shown that trading caravanas from Shensi in Northern China arrived at Bokhara as early as the year 114 B.C. (Dymock et al 1890)

"Riwas" was known to the ancient Persians and the same name is still applied to a species of Rheum is called R. ribes.

Ibn-e-Sina (978-1023 AD) noticed both the plant "Ribas" (Riwas, Persian) and the drug "Rewand" (Rawand, Persian). "Mesue" (Masih), early in the 11th century, distinguished between Chinese and Khorasan Rhubarb (Dymock et al 1890). "Haji Zein-al-Attar" (1368 Hijri) considered "Rewand" to be the same as "Ribas". According to "Ibn-e-Jazla", there are two kinds of Rhubarb, Chinese and Khorasan Rhubarb, and that the later is known as `Rewand-aldawaab', and is used in veterinary practice, whilst the Chinese is reserved for human beings. The later is the best kind, and when powdered, attain a saffron colour. The fractured surface has the grain of a cow's hump and is friable; It is called `Rewand-i-lahmi' (meaty Rhubarb), and should be in large pieces like a horse's hoof and not worm eaten (Dymock et al 1890).

While in view of `Dymock', there are three kinds of Rhubarb in his experience as Chinese, Khorasan and Indian Rhubarb. It is also reported with the reference of "Noor Karim", the author of `Makhzan-al-Advia' that the Rhubarb is called Riwas, Riwaj and Chukri in Persian language. Rhubarb is an herbaceous plant, a cubit in height, from the centre spring one or two flattened stems, two fingers by one finger in thickness, having a pubescent bark, the lower portion of which is purplish and the upper green, like the stem of a lettuce. Internally the stem is white, soft and juicy; it has a sour and some what astringent taste. The top of the stem is branched, and between the branches are green rough bracts. The flowers are red, and have a slightly acidic and sweetish taste. The plant grows in the cold snowy mountains; the best is the Persian, white, delicate, succulent and subacid, with a stout tall stalk. The root of this plant is Rhubarb (Rewand), and it is called "Ribas-i-Mu' amiri", because one Mu'ammir of Nishapur was the first to discover this (Dymock et al 1890). `Abu Rehan Baruni' has also described the name of Bekh-e-Ribas. The plant of Rhubarb was introduced to Europe in 1867, and limited cultivation led to further names such as English, German, Bucharest, Dutch and French Rhubarb (Stuart 1979).

The plant of Rhubarb was known in old Ayurveda with the name `Amlavetes', but they did not know about its rhizome and root and its actions. Firstly Rhubarb was described in Ayurveda by `Revan' in `Arqe-Prakash', who actually has taken it from Unani literature (Bedi 1994).

The Garden Rhubarb (R. officinalis) was introduced to Western Europe in 1608. It is grown for its edible leaf stalks. The flowering branches of R. ribes are eaten and the root is used in colouring leather. R. tetaricum is found in Hari-rud valley, known as `Rewash-i-dewana' or Fools Rhubarb (Stuart 1979).

The Rhubarb found in the Indian market is of a very inferior kind, in long stick pieces, shipped to Calcutta and Bombay from the Eastern ports. It comes from China and has hardly any aroma, a bitter taste, and having slightly purgative action. When fresh, it is covered with a yellow dust, like ordinary Rhubarb. None of the commercial Rhubarb known as East India Rhubarb is imported into Bombay unless specially ordered from China, Bombay druggists, native and European usually obtain their Rhubarb from London. On account of its low price, the former always import English Rhubarb. In the Pharmacopoeia of India, the market sample of Rhubarb in India is attributed to R. emodi, R. moorcroftianum and R. webbianum. All Himalayan species are said to be of two kinds, large and small. The first kind so exactly corresponds with the stick Rhubarb imported from China, which we are of opinion that it was not Himalayan Rhubarb, whilst the second probably was of Indian origin. Trials made with Himalayan Rhubarb by `Prof. Royle' and `Mr. Twining' are reported to have been satisfactory, and `Hugh Claghoru', who furnished some interesting remarks on Himalayan Rhubarb, The rhizomes of Rhubarb in India are procured from R. emodi, R. webbianum, R. moorcroftianum and R. spiciforme. The pieces of rhizomes of above mentioned plants are sold in mixed form in Indian market as Revand chini.

R. palmatum is the main source for Rhubarb in China, and it is used most commonly as medicine there. It is also called Chinghai Rhubarb. In Sikkim, Rhubarb is procured from R. palmatum, R. nobile and R. undulatum (Anonymous 1972, Orta and Garcia Da 1895).

TYPES AND SPECIES OF REVAND

The classical Unani literature survey revealed that a number of species of Revand and their varieties were known to the Unani physicians. They classified the Revand, on the basis of the colours, origin and morphological features of the plant. Some are reported in the literature, as Revand Chini, Revand Turki, Revand Khurasanee (Revand Dawaab), Revand Shammi (Revand Jabli), Revand Hindi, Revand Rusi, Revand Franceece, Revand Japanee, Revand Farsi, Revand Junji (Black Revand), Ribas-e-Pahan (R. palmatum), Ribas-e-Tibbi (R. officinale), Ribas-e-Barbari (R. rhaponticum), Ribas-e-Sulab (R. compactum) Ribas-e-Mawaaj (R. undulatum) (Aquiqi 1960, Khan GJ 1915, Nafees Bin Auz 1342 H, Ghani MN 1911)

1.According to Unani physicians, the term Revand is applied only for Revand Chini, Revand Junji, Revand Turki or Farsi Revand Shammi (Aquiqi 1960, Ghani,1911, Nafees, 1342 H). Ibn-e-Baitar (1197-1248) mentioned four types of Revand e.g. Revand Chini, Revand Turki, Revand Junji and Revand Shammi. In which Revand Shammi is not imported from China and has unlike action of rest of three (Ghani MN 1911). According to Minhajud-dukkan's author that Revand Turki was considered as New Revand and Rhubarb is called as Old Revand (Kareem 1879).

Among these Rhubarb Chini was considered the best one, and Indian Rhubarb stands after this (Ghani 1911). Revand Khurasanee (Revand dawaab) is used as veterinary medicine. Presently three types of Rhubarb are available which are as under:

1.Chinese Rhubarb

The rhizome of either R. palmatum or R. officinale are considered as Chinese Rhubarb. Important commercial varieties are Shensi, Canton and high dried. The shensi is got from R. palmatum. It is considered as the best type, which is some times marketed under the name as Chinghai.

2.Indian / Himalayan Rhubarb

It consists of dried rhizome of (R. emodi, or R. webbianum, or R. moorcroftianum or R. spiciforme).

3.Rhapontic Rhubarb

The rhizomes of R. rhaponticum are considered as Rhapontic Rhubarb. It causes gripe and is not official in the Pharmacopoeias (Anonymous 1972). It contains rhaponticin, a stilbene

derivative, having estrogenic action (Shah and Quadry 1991).

The genus rheum comprises about 50 species (Evans Williams Charles 1989). In which some are used medicinally, some for culinary purposes, few others are grown as ornament and some are grown as vegetable (Anonymous 1972).

MIZAJ or Temperament

A lot of difference of opinion is found among the Unani scholars regarding Mizaj or temperament of Revand chini. Most of the scholars categorized it as Murakkabul Quwa and Hot and Dry in II degree (Ghani 1911, Ibn-e-baitar 1987, Razi 1980). While some Unani scholars described it as Hot and Dry in I degree (Ghani 1911, Khan 1313 Hijri), and some mentioned in III degree (Aquiqi 1960, Ghani 1911). According to some other scholars it is hot in III degree and Dry in I degree (Ghani 1911). It has been also reported as Cold and Dry in II degree (Momin 1320 Hijri).

Nephroprotection:

Multiple intrinsic mechanisms modulate intracellular free radical metabolism. They affect processes involved in both the generation of free radical metabolites and other intermediates and the disposition of these compounds formed. Superoxide dismutase metabolise superoxide but produces hydrogen peroxide. Catalase enhances the metabolism of hydrogen peroxide to water and molecular oxygen, reducing the availability of hydrogen peroxide to participate in the Fenton reaction (Freeman and Crapo 1982).

Glutathione (GSH) is a tripeptide with the aminoacid sequence gamma glutamyl cysteinglycine. It is the most abundant cellular peptide and the major non protein thiol of most cells (Meister and Anderson 1983). Roles for glutathiones as an intracellular anti oxidant and participant in detoxification reactions in the kidney and other tissues are well documented and it is a widely held view that a critical level of cellular glutathione is necessary for the prevention of oxidant damage to cellular lipids and proteins.

GSH acts to limit oxidant injury by serving as a substrate for glutathione peroxides in the metabolism of hydrogen peroxide and lipid hydroperoxides (Little and O'Brien 1968), is involved in the antioxidant effects of vitamin E and can interact directly with free radical matabolites. Conjugation of glutathione mediated by glutathione S transferase or direct interaction with reactive compounds is an important detoxification mechanism and can also contribute to toxic activation of some compounds.

Vitamins E, alpha tocopherol is a scavenger largely localized with in membranes because of its high lipid solubility and thus plays a special role at the critical membrane lipid targets of free radicals (Pascoe and Reed 1989). Tocophenyl radicals formed during reduction of lipid peroxyl radicals to lipid hydroperoxides by Vit E are converted back to alpha-tocopherol by GSH with the participation of a labile membrame factor. Ascorbic acid can also scavenger free radicals and act co operatively with Vit E (Pascoe and Reed 989).

Antioxidants:

A number of agents with major effects on metabolic activation and free radical metabolites have been widely used as probes for testing the contribution of these process to various forms of injury. DMSO, mannitol and dimethylurea are hydroxyl radical scavengers Deferoxamine chalates Fe2+required for the Fenton reaction (Gutteridge et al 1979) and can also scavenge peroxyl and alkoxyl radicals at higher concentration. N, N' diphenyl p-phenylene diamine (DPPD) has been widely used as an antioxidants but also can inhibit microsomal cutochrome P450 bio activation reactions. Interpreting the effect of agents altering intracellular toxic activation and free radical metabolism is complex because of several factors.

1)Differential effects in liver and kidney may alter drug distribution. Increased hepatic metabolism may decrease delivery to the kidney, thus

reducing toxicity on the basis. This occurs with cyclosporine

2)Within a given tissue competing metabolic pathways may be evoked to various degrees so that toxin activation and inactivation are simultaneously increased.

3)The agents used may affect the nature of toxicity by means of processes that are independent of toxic activation or free radical production e.g.: alteration of cellular toxin transport.

R.officinale extract treatment on urine composition in rats with adenine-induced renal failure was studied. Administration of the rhubarb (R.officinale) extract markedly increased the urinary excretion of both urea and creatinine, indicating an improvement of renal clearance in the uremic state. A number of significant differences in the amino acid levels in the urine were observed. Among the essential amino acids, the urinary out puts of threonine, phenylalanine, leucine, and methionine were remarkably lower in the rhubarb extract treated group than in the control group. Out puts of in essential amino acids were also strikingly reduced after the treatment. The amount of urinary Ca was significantly reduced in the rhubarb extract treated rats, while urinary inorganic phosphate was significantly elevated. A marker decrease of 2,8-dihydroxyadenine excretion in the urine was noticed. However no changes were seen in the urinary excretion of protein, glucose, Na and K through out the experimental period [Yokozawa, et al 1984]. It decrease of blood urea nitrogen, ammonia nitrogen in the portal vein, urea concentration in hepatic tissue, Gln, Lys, Thr, Ala, Gly, Ser, Glu, Pro, Arg, Tyr, Cit, Asp amino acids etc. in serum while significant increase of Glu, and Asp, in hepatic tissue were observed. The mechanism of the blood urea nitrogen decreasing activity of rhubarb extract was proposed on the basis of the present results. [Yokozawa, et al 1987; Yokozawa, et al 1986]. The effect of each of several tannins purified from Rhei rhizoma on serum constituents were investigated in rats with adenine induced renal failure. Blood levels of urea nitrogen, methylguanidine (MG), and guanidinosuccinic acid (GSA) were significantly decreassed in rats given (-)-epicatechin 3-O-gallate at a dose of 2.5,5 or 10 mg/kg body weight / day for 24 days. The creatinine (Cr) levels was also significantly decreased in rats given 5 mg 10 mg of this compound. A significant decrease in urea nitrogen, MG, and GSA was found in rats given 6.25 mg of procyanidin B-2 3,3/-di-O-gallate. However unlike the former two components the administration of 12.5 mg of procyanidin C-1 3,3//-tri-O-gallate produced a considerable or significant increase in blood levels of urea nitrogen, Cr, MG, and GSA. RG-tannins had a weaker overall effect on serum constituents excepts for GSA in comparison with the corresponding effect of (-)-epicatechin 3-O-gallate and 6.25mg of procyanidin B-2 3,3/-di-O-gallate. Rhatannin tended to increase the serum nitrogen constituents [Yokozawa, et al 1991, Yokozawa, et. al. 1995]. The glomerular filtration rate, renal plasma flow and renal blood flow were significantly increased in rats given (-)-epicatechin 3-O-gallate at a dose of 5 or 10 mg/kg body weight/day for 24 days. Administration of 5 mg of procyanidine B-2 3,3/-di-0-gallate also led to a significant increase in renal functional parameters. However unlike the former two components, procynidin C-1 3,3/,3//-tri-O-gallate caused aggravation of renal function. [Yokozawa et al 1993].

Rat renal tubules were isolated and grown in culture medium. The effects of Rheum officinale (RO) on the proliferation of renal tubular cells were investigated. In culture the addition of the sera obtained from the rat fed with RO inhibited significantly the proliferation of renal tubular cells and the effect become even stronger with the increase of the dosage or the long time of administration of RO to the rat. The ingredient of RO emodin added directly to culture medium suppressed the proliferation of renal tubular cells

in a dose dependant manner, as measured by the uptake of radio labelled thymidine. This observation may help to explain the beneficial effects of RO in the treatment of chronic renal failure. [Yokozawa, et. al. 1986, Zheng, 1993].

In order to explore the therapeutic potential of traditional Chinese medicinal herbs on the progression of experimental chronic renal failure (CRF), the effect of orally administered rhubarb extract on the course of CRF in rats submitted to subtotal nephrectomy (SNx) was studied. Adult male wistar rats were submitted to either a SNx (n=18) or a sham operation (n=10). Thirty days after SNx, nine SNX and five sham operated rats were given aqueous rhubarb roots extract (150 mg/day) in drinking water. The rats were followed up for 120 days. Rhubarb treatment had no effect on the systemic hypertension observed in SNx rats. Rhubarb tested SNx rats had significantly less proteinuria 90 days (172 □ 63 mg / 24h) and 120 days (228 □ 92 mg/24h) after SNx. When comparable to untreated SNx controls (day 90, 246 □ 80 mg/24h), (120, 335 □ 113 mg / 24h) (P <0.05). Renal function was compared in rhubarb treated and untreated SNx rats. However at sacrifice the severity of glomerulosclerosis was significantly reduced in SNx rats treated with rhubarb (2.03 □ 0.44; SNx controls, 2.58 □ 0.53; P < 0.05). The difference in tubulointerstitial scarring between the two groups did not reach significance. Our results suggest that rhubarb extract reduces proteinuria and the severity of glomerulosclerosis in rats with remnant kidneys. [yokozawa, et. al. 1984, Zhang and Nahas, 1996].

In clinical trial it was also found that some Chinese herbal drugs containg Rheum E and angiotensin converting enzyme inhibitor, showed that the progression rate of renal failure, calculated by regression analysis of 1/ S. cr vs time, was found to be retarded after. Treated with the increase regression co efficient (b value). S cr levels and blood urea nitrogen were kept stable or fell slight. Albumin raise during the follow up period (P < 0.05) in the treated patients being more marked in both Rheum E and Rheum E + captopril groups Uraemia symptoms of nausea, anorexia improved in most of the treated patients. It is concluded that long term low dose Rheum E taken orally is beneficial to CRF. Its effect is better than that of captopril. The regime of Rheum-E is a preferable choice in the long term treatment for preventing progression of CRF. [Zhang, et al 1990, Li & Liu 1991; Kang et al 1993, Ji. et al 1993].

It is well known that diet therapy is effective for inhibition of the advancement of chronic renal failure. Rhubarb, which can improve nitrogen metabolism, may allow delay in the introduction of the hemodialysis. [Sadana, 1996]

Higher allopurinol dose is independently protective against incident renal failure in the elderly allopurinol users. A longer duration of allopurinol use may be associated with lower risk of incident renal failure. (Singh & Yu 2017).

Petroleum ether, ethyl acetate and n-butanol extracts of rhubarb delayed development and/or reversal the disorders in key metabolites associated with adenine-induced CRF in a rat model (Zhang, et. al. 2015, Zhang, et. al. 2016).

Rhein possesses various pharmacological activities, including anti-inflammatory, antioxidative, antitumor, purgative effects, and so on. Rhein showed nephroprotective on urate nephropathy induced by adenine and ethambutol in mice (Meng, et. al. 2015).

emodin(a rhubarb anthraquinone) had ameliorated cisplatin induced nephrotoxicity in rats by treatment significantly increased urine volume and N-acetyl-β-D-glucosaminidase activity and significantly decreased osmolarity and protein concentrations (Ali, et. al. 2013).

A Chinese herbal preparation WH30+ composed of Rheum Palmatum, Salvia Miltiorrhiza, Cordyceps Sinensis, Leonurus Sibiricus, Epihedium Macranthum, Radix Astragali, and Radix Codonopsis Pilosulae, had significantly greater creatinine clearance than those without treatment. The results of the study show that

WH30+ is more effective in the prevention of acute renal failure than chronic renal failure (Ngai, et. al. 2005).

The renal effects of water-soluble (W-S) and water-insoluble (W-INS) portions of the alcoholic extract of Revand Hindi (Rheum emodi) were improved the renal function by protecting S2 segment of proximal tubule nephrotoxicity induced by metals viz cadmium chloride and mercuric chloride in rat models (Alam, et. al. 2005).

Musleh (Correctives):

In Unani System of Medicine, the correctives for the untoward effects of Rhubarb are mentioned as - Unnab, Samag-e-Arabi (Hakeem 1312 Hijri,Hanfi) Behdana Sheeren (Haleem 1948, Kabir-uddin 1951) Gond Kateera, Babool, Water extract of Kasni, Zarishk or Banslochan (Aquiqi 1960, Ghani 1911).

Emodin (a rhubarb anthraquinone) Emodin augmented the cisplatin-induced inhibition of antioxidant enzymes (catalase, glutathione peroxidase, glutathione S-transferase, glutathione reductase and superoxide dismutase) (Waly, et. al. 2013).

Chrysophanol of Rhubarb protected brain tissue damage during cerebral ischemia/reperfusion is accompanied by NALP3 inflammasome activation. Chrysophanol could inhibit the activation of NALP3 inflammasome and protect cerebral ischemic stroke (Zhang, et. Al. 2014).

References:

1. Alam MM, Javed K, Jafri MA. (2005). Effect of Rheum emodi (Revand Hindi) on renal functions in rats. J Ethnopharmacol., 96(1-2): 121-125.
2. Ali BH, Al-Salam S, Al Husseini IS, Al-Lawati I, Waly M, Yasin J, Fahim M, Nemmar A (2013). Abrogation of cisplatin-induced nephrotoxicity by emodin in rats. Fundam Clin Pharmacol.27(2):192-200.
3. Anonymous (1972). "The Wealth of India" Vol-IX, Publication and Information Directorate, CSIR, New Delhi, 3-6.
4. Aquiqi MAM, (1960) "Jame-ul-Aqaqeer", Vol-II, Kamil Book Depot, Lahore; 299-314.
5. Bedi R, (1994). Revand chini se hum Parichit thai; Sachitra Ayurved. 47 (6):423-425.
6. Dymock, W., Warden, C.J.H., Hopper, D., (1890), Pharmacographia Indica, A History of the principal drugs of vegetable origin, (Part III), M/S Bishen Singh Mahendra Pal Singh, Dehradun & M/S Periodical Expert, Delhi: 152-157.
7. Evans, W.C., (1989) "Trease and Evans'Pharmacognosy", (XIII edition) Bailliere Tindall, 24-28 Oval Road, London, NW1 7DX: 408-413.
8. Freeman BA, Crapo JD.(1982) "Biology of disease : Free radicals and tissue injury". Lab invest; 47: 412.
9. Ghani MN, (1911) 'Khawasul Advai: VolII, Kashmiri Bazar, Rawalpindi, Lahore, 23-25.
10. Gutteridge JM, Richmond R, Halliwell B. (1979) "Inhibition of the iron catalyzed formation of hydroxly radicals from superoxide and of lipid peroxidation by desferrioxamine". Biochem J; 184 : 469.
11. Hakeem MA, (1312 Hijri) **"**Bustanul Mufradat", Karkhana Jamaiul Advia, Lucknow: 183.
12. Haleem M Abdul, (1948) "Mufradar-e-Azzizi" Sahitya Mandir Press Limited, Lucknow, 33, 80.
13. Ibne-Baitar (1987), "Aljamaiul Mufradat-ul Advia Wal Aghzia" V-II (Urdu Transla) CCRUM, New Delhi: 275-282.
14. Ji SM, Li LS, Ji DX, (1993) "Effects of baoshen pill in treating chronic renal failure with long-term hemodialysis." Chung Kuo Chung His I Chieh Ho Tsa Chih**.** Feb: 13 (2) : 71-73, 67.
15. Kabir-uddin M, (1951) "Makhzanul Mufradat" (Kitabul Advia), Shaikh Mohd Basheer and Sons, Lahore, 309.
16. Kang Z, Bi Z, Ji W, Zhao C, Xie Y, (1993) "Observation of therapeutic effect in 50 cases of chronic renal failure treated with rhubarb and adjuvant drugs." J Tradit Chin Med. Dec 13 (4) 249-252.
17. Kareem N, (1879) "Tarjuma Makhzanul Advia Urdu" Vol-I Translated by Udru Darul Shifa, Munshi Naval Kishore, Kanpur; 256-257.

18. Khan Ghulam Jeelani, (1915) "Makhzanul Advia Doctori" Vol-II, Naval kishore Limited Press, Lahore; 2008-2017.
19. Khan M Azam, (1313 Hijri) **"**Muheet-e-Azam**"** Vol-II, Part-II, Nizami, Kanpur: 76-81.
20. Li LS, Liu ZH, (1991) "Clinical and experimental studies of rheum on preventing progression of chronic renal failure." Chung His I Chieh Ho Tsa Chih Jul ;11 (7) : 392 - 396' 387.
21. Little C, O'Brien PJ. (1968) "An intracellular GSH peroxidase with a lipid peroxide substrate". Biochem Biophys Res Commun; 31: 145.
22. Meister A, Anderson ME. (1983) "Glutathione". Ann Rev. Biochem; 52 : 711.
23. Meng Z, Yan Y, Tang Z, Guo C, Li N, Huang W, Ding G, Wang Z, Xiao W, Yang Z. (2015). Anti-hyperuricemic and nephroprotective effects of rhein in hyperuricemic mice. Planta Med. 81(4):279-85.
24. Momin M, (1320 H) "Tohfatul Momenin" Munshi Naval Kishore, Lucknow: 130.
25. Nafees Bin Auz, (1342 Hijri) "Urdu Tarjuma-e-Nafeesee" transla. By S. Abid Hussain. Munshi Naval Kishore, Lucknow; 103-105.
26. Ngai HH, Sit WH, Wan JM. (2005). The nephroprotective effects of the herbal medicine preparation, WH30+, on the chemical-induced acute and chronic renal failure in rats. Am J Chin Med. 33(3): 491-500.
27. Orta Garcia Da, (1895) "Colloquies on the simple and drugs of India" (Trans in English) Henry Southern and Co. London: 390-392.
28. Pascoe GA, Reed DJ. (1989) "Cell calcium, vit E and the thio redox system in cytotoxicity". Free Radio Biol Med; 6: 209.
29. Razi Zakaria (865-925) (1980) **"**Kitabul abdal**"** Translated and published by CCRUM, New Delhi : 52.
30. Sadana H, (1996) "Study on the clinical effect of rhubarb on nitrogen-metabolism abnormality due to chronic renal failure and its mechanism." Nippon Jinzo Gakkai Shi. Aug. 38 (8): 379-387.
31. Singh JA, Yu S.(2017). Are allopurinol dose and duration of use nephroprotective in the elderly? A Medicare claims study of allopurinol use and incident renal failure. Ann Rheum Dis. 76(1):133-139.
32. Shah CS, Qadry JS, (1991) **"**A Text Book of Pharmacognosy**"**, Baba Lal & Somchand Shah, Ahmedabad; 88-89.
33. Stuart M. (1979), The Encyclopaedia of Herbs and Harberium. Orbis Publishing. London: 93: 111-252.
34. Waly MI, Ali BH, Al-Lawati I, Nemmar A. (2013) Protective effects of emodin against cisplatin-induced oxidative stress in cultured human kidney (HEK 293) cells. J Appl Toxicol., 33(7):626-30.
35. Yokozawa T, Dong E, Chung HY, Oura H, Nagakawa H, (1997). "Inhibitory effect of green tea on injury to a cultured renal epithelial cell, LLC-PK " Bioscience ,Biotechnology and biochemistry, 61(1): 204-206.
36. Yokozawa T, Dong E, NakagawaT, Kashiwagi H, Nakagawa H, Takeuchi S Chung HY (1998) "In vitro and in vivo studies on radical scavenging activity of tea." Journal of Agricultural and Food Chemistry, 46(6): 2143-2150.
37. Yokozawa T, Fujioka K, Oura H, Nonaka G, Nishioka I, (1991). "Effcets of rhubarb tannins on uremic toxins." Nephron 58(2): 155-160.
38. Yokozawa T, Fujioka K, Oura H, Nonaka G, Nishioka I, (1993). "Effcets of rhubarb tannins on renal failure." Nippon Jinzo Gakkai Shi. Jan. 35(1): 13-18.
39. Yokozawa T, Fujioka K, Oura H, Tanaka T, Nonaka G, Nishioka I. (1995). "Confirmation that tanin-containing crude drugs have a uraemic decreasing action". Phytotherapy Reasearch. 9(1): 1-5.
40. Yokozawa T, Suzuki N, Oura H, Nonaka G, and Nishioka I, (1986). "Effect of extracts obtained from rhubarb in rats with chronic failure". Chem. Pharm. Bull. 34(11): 4718-4723.
41. Yokozawa T, Suzuki N, Oura H, Nonaka GI, Nishioka I (1986) " Effects of extracts obtained from rhubarb in rats with Chronic renal failure." Chem. Pharm. Bull 34(11): 4718-4723.
42. Yokozawa T, suzuki N, Zzhang PD, Oura H, and Nishioka I, (1984). "Effect of orally administered rhubarb extract in rats with chronic renal failure". Chem. Pharm. Bull. 32, 4506-4513.

43. Yokozawa T, Zheng PD, Oura H, Nishioka I, (1984) "Urine compositiion inrats with adenine induced renal failure during treatment with rhubarb." Chem.Pharm. Bull. 32(1): 205-212.
44. Zhang F, (1993) "Effect of Rheum officinal on proliferation of renal tubular cells in vitro." Chung Hua I Hsueh Tsa Chih Jun, 73 (6): 343-345, 380-381.
45. Zhang G, El Nahas AM, (1996) "The effect of rhubarb extract on experimental renal fibrosis." Nephrol Dial Transplant, 11(1): 186-190.
46. Zhang JH, LiLS, Zhang M, (1990). "Clinical effects of rheum and captopril on preventing progression of chronic renal failure." Chin Med J Oct, 103(10): 788-793.
47. Zhang N, Zhang X, Liu X, Wang H, Xue J, Yu J, Kang N, Wang X. (2014). Chrysophanol inhibits NALP3 inflammasome activation and ameliorates cerebral ischemia/reperfusion in mice. Mediators Inflamm, :370530.
48. Zhang ZH, Vaziri ND, Wei F, Cheng XL, Bai X, Zhao YY (2016). An integrated lipidomics and metabolomics reveal nephroprotective effect and biochemical mechanism of Rheum officinale in chronic renal failure. Sci Rep. 23;6: 22151.
49. Zhang ZH, Wei F, Vaziri ND, Cheng XL, Bai X, Lin RC, Zhao YY (2015). Metabolomics insights into chronic kidney disease and modulatory effect of rhubarb against tubulointerstitial fibrosis. Sci Rep. 28;5:14472.