

ROLE OF PHYTOCHEMICALS IN DIURESIS MANAGEMENT

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ABSTRACT

Diuretics are one of the main classes of medicine used for the management of heart failure, edema, hypertension and always improve patient's quality of life. Diuretics also known as water pills or fluid pills that increase urine production in kidney by promotes the removal of salt and fluid from the body. Herbal medicine possess large number of plant derived chemical entities, products and active substances which have been proved highly effective and efficacious in vast number of diseases. The use of herbal medicine is becoming popular due to toxicity and adverse effects of allopathic drugs. Mono and poly herbal preparations have been used as diuretics. The phytochemical study revealed that plant contain active constituents like alkaloid,

flavonoid, saponin, triterpenoid, glycosides, nitrates are responsible for the diuretic activity. The diuretic activity produced by stimulating regional blood flow, initial vasodilation or by producing inhibition of tubular reabsorption of water and anions both results in diuresis.

KEYWORDS: Diuretics, Herbs, Medicine, Phytoconstituents, Mechanism.

INTRODUCTION

Diuretics are among the most important therapeutic tool used extensively and successfully for the treatment of several medical disorder in worldwide. The word diuretic has originated from, diu (through) oyrlih (to urinate), and a diuretic is defined as any substance that increases urine flow and thereby water excretion. Diuretics are among the most commonly

used drugs and the majority act by reducing sodium chloride reabsorption at different sites in the nephron, thereby increasing urinary sodium, and consequently, water loss.^[1] Diuretic have been recommended as first line treatment of hypertension and also valuable in the management of hypovolemia, electrolyte disorders, chronic and acute renal failure, cirrhosis of liver, pulmonary congestion and peripheral edema. One of the important and well - documented uses of plant -products is their use as diuretic agents. Plant medicine was commonly used in traditional treatment of some renal diseases, many showed significant diuretic activity.^[1]

Traditional diuretics, such as loop diuretics and thiazide diuretics, specifically inhibit the $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ cotransporters in the thick ascending limb and the Na^+/Cl^- cotransporters in the distal convoluted tubules, respectively. Then, by inhibiting NaCl reabsorption, the ability to concentrate urine is reduced, and a large amount of urine close to isosmotic conditions is excreted. Long-term use of these diuretic drugs can cause electrolyte disturbance, especially deficiency of blood potassium, which will seriously affect the normal physiological functions of the body, such as causing hyperglycemia, hyperlipidemia and even life threatening complications.^[2]

The use of synthetic compounds has significant drawbacks, such as increasing cost, and may leads to negative health consequences. As a good alternative medicinal plants replaced by synthetic medicines, as natural effectiveness and non-toxic compounds. Medicinal plants are cheaply available and have little side effects. The consumption of herbal medicine provide an alternative treatment for alleviating a number of health problems.^[3] Medicinal plants can be important sources of previously unknown chemical substance with potential therapeutic effects. Herbal medicine use is becoming popular due to toxicity and adverse effects of allopathic drugs. Mono and poly-herbal preparations have been used as diuretics. This leads to sudden increase in the number of herbal drug manufactures. Herbal medicine have been the most commonly prescribed medications for diuretics.^[4] The medicinal value of these plants lies in some chemical active substances that produce a definite physiological action on the human body. The most important of these chemically active (bioactive) constituents of plants are: saponin, glycosides, alkaloids and flavonoid compounds. Many of these indigenous medicinal plants are also used for medicinal purposes.^[5]

In these study we are reviewing some medicinal plants containing phytochemicals that have potent diuretic activity.

Phytochemical in the management of diuretics

Triterpenes

Triterpenes comprise one of the most interesting groups of natural products due to their diverse Pharmacological activities. Triterpenes are widely distributed in plant kingdom. They are produced in plant as secondary metabolites and have varied biological activities. Below some important class of triterpenes reported with their diuretic activity.

Alismatis rhizome (AR), the dried rhizome of *Alisma orientale* Juzepak belongs to the family Alismataceae. It is a natural medicine widely cultivated in China, Japan, Korea, India and Europe. Traditionally it possess Diuretic, Hyperlipidemic, Inflammatory, Antitumoral actions and has been used for treating Dysuria, edema, urinary tract infection, retention of fluid and phlegm and vertigo for more than 1000 years. The ethanol extract of *Alisma orientale* and alisol A 24-acetate exerts diuretic effects on animals, this ethanol extract contains mainly terpenoids, including alisol B 23-acetate, alisol B, alisol A 24-acetate, alisol A, and alisol C-23 acetate. Therefore, alisol B 23- acetate, alisol B, alisol A-24 acetate, alisol A, alisol C-23 acetate these five main triterpenes may be the active compounds responsible for the observed diuretic effect. Diuretic activity of triterpenes are associated with the significant increase of Na^+ , Cl^- , and K^+ Excretions. Modern Pharmacology proved that 23-acetate alisol B and alisol A 24-acetate were the main ingredients contributing diuretic activity of *Alismatis* rhizome.^[6]

Alkaloids

Alkaloids are one of the most abundant and diverse group of secondary metabolites found at a minimum concentration in almost all plants. Well known alkaloids include morphine, strychnine, quinine, ephedrine and nicotine. Majority of the alkaloids possess diuretic effect.

Berberine, an isoquinoline alkaloid is obtained from *Cissampelos pareira* plant. It is an extensively spreading, glabrous, pubescent, perennial climbing shrub found all over India and belongs to the family Menispermaceae. In Ayurveda system of medicine, the leaves and roots are used in the treatment of ulcers and diarrhea. Plant used in the treatment of urinary tract infection since it is considered as antiseptic, use for inflammation of muscles, snakebite, rheumatism, dysentery, constipation and menstrual problems. The major constituents of roots of *Cissampelos pareira* include Pelosin, O-methylcurine, l-curine Cissamine, Cissampareine, Hyatin, Bebeerine, Cycleanine, Tetrandine and Berberine, Cissampeline, Cissampoline, Dicentrine, Insularine, Pareirine, Hyatinine, Pareirubrine A, Pareirubrine B, Pareitropone, Norimeluteine, Cissampeloflavone, D-Quercitol and Grandirubrine. Phytoconstituents like

berberine or pelosine are already reported for this diuretic activity. The plant *Cissampelos pareira* was also reported with berberine. When tested for diuretic activity, Berberine increased urine excretion in the rats. Berberine increase urine volume by increase in the Na^+ , K^+ excretion suggesting that Berberine induced diuresis caused by its saluretic effect.^[7]

Cyclea peltata (Lam) Hook. f. & Thoms belongs to the Family Menispermaceae. It is a common plant in the west coast of India. The leaves of *Cyclea peltata* were being used traditionally as coolant, antidandruff, antipyretic, diuretic, treatment of herpes. The leaves of *Cyclea peltata* are found to contain Alkaloids such as cycleanine, bebeerine, hayatinin, hayatidin and hayatin. Five bisbenzylisoquinoline alkaloids like cycleapeltine, cycleadrine, cycleacuine, cycleanorine and cycleahomine chloride have been isolated from the roots of *Cyclea peltata*. Based on the excretion pattern of water, Na^+ and K^+ , it appears that the active principle present in *Cyclea peltata* having furosemide like activity. The study proved that diuretic activity associated with the presence of isoquinoline type alkaloids.^[8]

Acorus calamus L. (Family: Araceae) commonly known as 'sweet flag', a well-known medicinal plant of the Indian medicinal system. The major chemical constituents of *Acorus calamus* rhizome are alkaloids, flavonoids, gums, lectins, mucilage, phenols, quinone, saponins, sugars, tannins, and triterpenes. The essential oil components of rhizomes comprise mainly α -asarone, β -asarone, γ -asarone, isoeugenol, acorenone, iso-acorone, and Z-sesquilandulol and dehydroxy isocalamendiol.

Acorus calamus have been reported various pharmacological activities like antidiabetic, antiproliferative and immunosuppressive, antidiarrheal, hypolipidemic, antioxidant, diuretic, insomnia, epilepsy, loss of memory, and nephroprotective activities. Extract of *Acorus calamus* administration increases dose dependent excretion of both Na^+ and K^+ electrolytes. The action produced are similar to furosemide. The study revealed that rapid and acute diuretic activity associated with quinone like alkaloid and other phytochemical like steroids, tannins, phenolic compound, terpenoids and flavonoids.^[9]

Moringa stenopetala commonly known as cabbage tree belongs to the family Moringaceae. Mainly associated with the treatment of malaria, antileishmanial, antitrypanosomal, antifertility, antidiabetic and other health problems. The phytoconstituents like tannins, flavonoids, saponins, coumarin and alkaloids are present in plant extract. *Moringa stenopetala* possess a palpable diuretic activity compared to furosemide and they act by

increase Na^+ and K^+ excretion. Tannin and flavonoid combination with alkaloid to produce apparent diuretic activity.^[10]

Flavonoids

Flavonoids are natural polyphenolic products that can be found in a variety of plants and fruits. Flavonoids can be further classified into flavones, flavonols and isoflavone. Certain flavonoids were found to exert their diuretic activity by binding with adenosine A_1 receptor associated with the diuretic action. Below are some important classes of flavonoids that possess diuretic effect.

Euphorbia granulata belonging to family Euphorbiaceae is native to north and tropical Africa, Iran, Pakistan, Palestine, North India, Afghanistan, Japan and China and is found to grow in plains and lower hills. The latex of *Euphorbia granulata* is internally used to expel intestinal worms and externally applied to snake bites and scorpion stings. Its latex is used as a purgative, anthelmintic and diuretic, as well as for its blood purifying characteristics in Saudi Arabia. It shows inhibitory effects against Human immunodeficiency virus (HIV-1) protease. As in herbal practice, it is used as a diuretic agent. Phytochemical evaluation shows that the plant contains secondary metabolites such as flavonoids, tannins and saponins. These active constituents either individually or in combination may produce diuretic effects. The flavonoid and tannins are associated with both diuretic and vasodilator effects. The phytochemicals act by increase in regional blood flow, vasodilation, or an inhibition of tubular secretion contributes to an increased urinary secretion. Any of these processes could be associated with diuretic effect of the extract. The flavonoids like quercetin, ferulic acid, and gallic acid possess diuretic effect.^[11]

Saffron is the most expensive spice in the world and consists of the dried stigmas of *Crocus sativus* commonly known as saffron, belonging to Iridaceae family, is a perennial plant widely cultivated in different parts of the world, mainly in Iran. Saffron is mainly used in food coloring and flavoring agent in the food industry and traditional cooking, but it is used in folk medicine as antispasmodic, carminative, stomachic, expectorant, aphrodisiac and cardiogenic. Recent pharmacological studies have reported that saffron extract has antitumor, anticonvulsant, antidepressant, anti-inflammatory, anti-hyperlipidemic, free radical scavenging and antioxidant properties. These activities are mainly related to its contents like picrocrocin, safranal and crocins. Picrocrocin is a monoterpene glycoside

precursor of safranal. Crocin, is a water soluble carotenoid. Crocins are crocetin esters with glucose, gentiobiose, neapolitanose or triglucose sugar moieties.

Saffron has a strong diuretic activity in terms of cumulative urine output, Hypernatremic, and Hyperkalemic activities. Diuretic activity of saffron was extremely rapid, almost similar to oral synthetic diuretic such as furosemide. The preliminary pharmacognostic study proved that diuretic activity mainly associated with the flavonoids and other polar compounds like carbohydrates, tannins, anthocyanins, alkaloids, and saponins.^[12]

Quercetin is a plant flavonoid from the flavonoid group of polyphenols obtained from *Hibiscus sabdariffa* L. belongs to the family Malvaceae traditionally used as an antihypertensive, diaphoretic and diuretic agent. Phytochemical study shows the presence of delphinidin-3-0-sambubioside 56.5 mg/g, cyanidin-3-0-sambubioside 20.8 mg/g, quercetin 3.2mg/g, rutin 2.1 mg/g, chlorogenic acid 2.7 mg/g. The polar extract of *Hibiscus sabdariffa* is also able to act as vascular smooth muscle relaxant by stimulation of NO/ cGMP endothelial pathway. Also, L-arginine produces systemic and renal vasodilation, which increased glomerular filtration rate. They acts on renal hemodynamics, that results in both increased GFR and an increase in renal filtration. The active constituents present in *Hibiscus Sabdariffa* able to acting as ACE inhibition, vascular smooth muscle relaxant and act as potassium sparing diuretic. Quercetin may contribute to the diuretic efficacy of the *Hibiscus sabdariffa* aqueous extract.^[13]

One of the most commonly used endemic species like *Smilax canariensis* wild (Smilacaceae) popularly known as zarzaparilla. Traditionally used as diuretic, laxative, hypoglycaemic, anticancer, cytotoxic, anticonvulsant, antioxidant, antidiabetic, antimicrobial, antiviral and anti-inflammatory properties. *Smilax* species contain mainly polar compounds like flavonoids and steroidal saponins. Plant contain large amount of polar fractions associated with the highest degree of diuretic activity. Polar compounds increase renal circulation and glomerular filtration rate which promote increased urine formation. Plant extract produce highest degree of diuretic activity due to presence of these compounds. Compounds act either individually or synergistically by stimulating regional blood flow or initial vasodilation their by cause diuretic effect.^[14]

Desmostachya bipinnata (Linn) is an official drug of Ayurvedic Pharmacopoeia, belonging to family Poaceae. It is distributed throughout India, Syria, Pakistan, Persia, and Africa. Mainly

used as astringent, aphrodisiac, galactagogue, analgesic, antipyretic, wounds, anti-inflammatory, anti-asthma, diuretic, dysentery, diarrhea, jaundice, vomiting, diabetes, urinary calculi and other disease of bladder and skin. Various phytochemical constituents such as carbohydrates, glycosides, alkaloids, flavonoids, terpenoids, tannins and phenolic compounds. The presence of polar compounds like flavonoids and terpenoids are responsible for diuretic activity.^[15]

Saponins

Saponin glycoside is widely distributed in plants. Saponin is used as a mild detergent and in intracellular histochemistry staining to allow antibody access to intracellular proteins. So it is used in hypercholesterolemia, hyperglycemia, diuresis, antioxidant, anti-cancer, anti-inflammatory and weight loss.

Vepris heterophylla is a medicinal plant used empirically in the mountainous massifs in the northern part of Cameroon for the treatment of various illnesses such as malaria and cardiovascular disorders. Phytochemical screening performed on crude extracts revealed the presence of several primary and secondary metabolites such as fatty acids, Anthraquinones, volatile oils, glycosides, saponins, tannins, coumarins and triterpenes. Phenolic compounds and sterols were also present in the extract. *Vepris heterophylla* contains several chemical compounds that could be partially or fully responsible for the increase of diuresis. *Vepris heterophylla* cause increase in both water and electrolyte excretion similar to furosemide which is known by its potential saluretic and diuretic effects. *Vepris heterophylla* may act as a loop diuretic which inhibit the Na^+ , K^+ , Cl^- Co-transporter system in the thick ascending loop of the nephron, thus increasing Natriuresis and kaliuresis. Also the extract induces the suppression of renal tubular reabsorption of water and electrolytes. The presence of flavonoids and alkaloids was significant. Presence of saponin cause significant diuretic activity.^[16]

Ampelozizyphus amazonicus Ducke, popularly known as “indian beer,” is a Rhamnaceae plant species found in the Amazonas State of Brazil. In folk medicine, its dried roots are used to prevent malaria. TLC and HPLC analysis showed the presence of saponins. They are jujube glycosides and glycosides of the new aglycon ampelozigenin. Jujubogenins are very unstable and can easily be converted to ebelin-lactone. *Ampelozizyphus amazonicus* chemically characterized by mixture of saponins as well as saponin free fraction. The extracts responsible for the diuretic activity may be sugar present in the saponin free fraction. The

other components observed in the extract are triterpenes of the lupane group such as lupeol, betulinic, and melaleucic acid. Saponins are mainly responsible for diuretic activity.^[17]

Ajuga remota Benth (Lamiaceae) is an erect rhizomatous pubescent herb that belongs to the genus *Ajuga* and growing in the grasslands of Kenya and other parts of East Africa. *Ajuga* have been used as a remedy for fever, toothache, dysentery, and high blood pressure, diabetes and hypertension, specifically for gastrointestinal disorders, and as an anthelmintic. Phytochemical screening shows the presence of phytoecdysteroids, neoclerodane- diterpines and diterpinoids, triterpines specific sterols, beta-sitosterol, gamma-sitosterol, cetyl alcohol, anthocyanidin-glucosides and iridoid glycosides, quinols, withanolid, flavonoids, tannins, triglycerides and essential oils. Two different mechanism by which diuresis could be achieved, one of which produces notable diuresis with a potassium sparing effect and another with very strong diuresis in which there is a clear tendency to lose the K^+ conservative effect. *Ajuga remota* extracts exerted diuretic effect by inhibiting tubular reabsorption of water and electrolytes. High dose of *Ajuga remota* extract produce similar action of furosemide. The extract always shows a carbonic anhydrase inhibition. The phytochemical study and pharmacological effects of *Ajuga remota* concluded that the effect may be produced by stimulating regional blood flow or initial vasodilation or by producing inhibition of tubular reabsorption of water and anions, both results in diuresis. Presence of these saponins indicates diuretic activity.^[18]

Withania aristata Ait. is one the endemic plant belongs to the family solanaceae. Aerial portions and fruit of these species have long been used as a scarring agent, antispasmodic, for rheumatic and eyes problems, otitis, as well as for insomnia, constipation and urinary pathologies. *Withania* can variously have anti-inflammatory, immunoprotective, anticancer, hepatoprotective, hypocholesteremic, antioxidant, antiartritic, anxiolytic, fungicidal, antibacterial, antimalarial and trypanocidal effects. Phytochemical study shows the presence of phytosterols, oleoresins, withaminol and withanolides. The diuretic effect is associated with the presence of polar nature active constituents like withanolides may be the main chemical protagonists of this activity. Diuretic activity of aqueous extract of *Withania aristata* are due to the high quantity of potassium found in the plant. Two different mechanism via *Withania aristata* acts, one of produces notable diuresis with a sparing of potassium and another with very strong diuresis in which there is a clear tendency to lose the potassium conservative effect. The effects may be produced by stimulating regional blood

flow or by producing inhibition of tubular reabsorption of water and anions. They act by initial vasodilation or inhibition of tubular reabsorption.^[19]

Nitrate

Nitrates have potential protective effect for body balance, improvement of disorder and playing an important role in physiological activity.

The diuretic properties of *Tribulus terrestris* are due to large quantities of nitrates and essential oil present in its fruits and seeds. *Tribulus terrestris* L (Zygophyllaceae) widely distributed in Iran and mediterranean region. It is a herbal remedy used for various medicinal purposes including the treatment of kidney troubles, particularly stones, diuretic, hypertension and hypercholesterolemia, immunomodulatory, antidiabetic, cardiogenic, hepatoprotective, anticarcinogenic activities. Its various parts contain a variety of chemical constituents like flavonoids, flavonol glycosides, steroidal saponins and alkaloids. Presence of nitrates and essential oil possess diuretic effect.^[20]

Glycosides

Cardiac glycosides and their aglycones, inhibit the cellular transport of sodium and potassium in a variety of tissues. In kidney, cardiac glycosides acts by inhibition of renal tubular absorption.

Plantago major cause greater urine flow by the diuretic effects of iridoid compounds. *Plantago major* widespread used medicinal plant from the Plantaginaceae family. Mainly used in the treatment of various diseases such as constipation, coughs, wounds, infection, fever, bleeding and inflammation. The pharmacological effects are produced by the constituents like flavonoids, polysaccharides, terpenoids, lipids, iridoid glycosides and caffeic acid derivatives. *Plantago major* has diuretic effects and also inhibit activity of angiotensin converting enzyme. Leaves extract contain active constituents like Aucubin and catalpol possess diuretic activity. Iridoid glycoside are the main active constituent's responsible diuretic activity. It possess diuretic activity due to the presence of Iridoid glycosides.^[21]

DISCUSSION

One of the important and well documented uses of plant products is their use diuretic agents. Mono and poly herbal formulation of herbal plants used as diuretic. The various parts of plants are used for the desired pharmacological action like leaf, stem, root, fruit, seed oils or

sometimes whole plant used. The extracts are obtained from the plant by using various solvents like acetate, chloroform, petroleum ether, methanol, ethanol, water. Triterpines of *Alismatis orientale*, alkaloids of *Cissampelos pareira*, *Cyclea peltata*, *Acorus calamus*, *Moringa stenopetala*, flavonoids of *Euphorbia granulate*, *Crocus sativus*, *Hibiscus sabdariffa*, *Smilax canariensis*, *Desmostachya bipinnata*, saponin of *Vepris heterophylla*, *Ampelozizyphus amazonicus*, *Ajuga remota*, *Withania aristata*, nitrates of *Tribulus terrestris*, glycosides of *Plantago major* might be involved in the mechanism of diuretic activity. Various phytochemicals responsible for diuretic activity includes alkaloids, glycosides, tannins, phenolics, coumarins, triterpenoids etc. These chemicals exerts the desired pharmacological effects on body and they act as natural diuretics. This active constituents either individually or combination may produce diuretic effects.

Diuretic activity of medicinal herbs are mainly associated with significant increase in Na^+ , Cl^- , K^+ excretions, they also stimulating regional blood flow or initial vasodilation their by cause diuretic effects. Renal vasodilation by which increased glomerular filtration rate and an increase in renal filtration. Sometimes herbal extract induces suppression of renal tubular reabsorption of water and electrolytes. Majority of extracts obtained from plant produce similar diuretic action of furosemide. so, adverse effects associated with traditional medicine avoided by the use of herbal medicines. Herbal medicines have no side effects and easily available so use of plant extracts are better compared to allopathic medicines.

CONCLUSION

This review summarizes the phytochemicals responsible for the diuretic activities of medicinal plants. Herbal medicine represents safety and security compared to synthetic medicine. The active constituents like flavonoid, glycoside, alkaloid, tannins and triterpenoids are responsible for diuretic activity. They act by stimulating regional blood flow, initial vasodilation or inhibition of tubular reabsorption. The review has included traditional uses and phytochemicals responsible for the pharmacological activity of plants. Herbal medicines produce similar diuretic action of furosemide drug. Herbal medications are cheaply available and free from adverse effects when compared to synthetic drugs. This review provide knowledge regarding herbal medicines used as diuretic.

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