Phytochemical Studies and Diuretic Effect of Matricaria Chamomilla Hydro Alcoholic Extract

Shaik. Meera Jasmine[1], M. Meena Kumari[2]

Department of pharmacology, Sri Sai Jyothi college of pharmacy, Vattinagula Pally, Gandipet Main Road, Hyderabad, Telangana 500075

Corresponding Author: Shaik. Meera Jasmine

Abstract

Use of plants as a source of medicine has been inherited and is an important component of the health care system in India. In the Indian systems of medicine, most practitioners formulate and dispense their own recipes, hence this requires proper documentation and research. The major hindrance in the amalgamation of herbal medicines into modern medical practices is the lack of scientific and 170 clinical data and better understanding of efficacy and safety of the herbal products. Herbs that stimulate the kidneys were traditionally used to reduce edema. In the present investigation one medicinal plants Hydro Alcoholic Extract of *Matricaria Chamomilla* . This current research work will be very beneficial in figuring out the *Matricaria chamomilla* leaves extract diuretic effect by determining the ions and electrolyte excreted by the animals using ion selective channel inhibition. Acute toxicity studies will be performed for the species *Matricaria chamomilla* which may have not shown any toxicity, which human body could be proved with the help of obtained study results. Diurectic activity of the herb *Matricaria chamomilla has* some beneficial effect on the selected animals, the herb *Matricaria chamomilla* may be selected for the further molecular level studies, *invivo* and *invitro* models are neccssary to get the complet information of the drug Matricaria chamomilla before using the plant in human volunteers.

Key words: Phytochemical Studies, Diuretic Effect, Matricaria Chamomilla, Hydro Alcoholic Extract

INTRODUCTION:

Water constitutes about 60% of the average adult body weight and is responsible for many physiological processes in the human body. Thus, fluid and electrolyte homeostasis is critical for human survival, as exemplified by the potentially devastating consequences of fluid imbalance. The balance of total body fluid is an extremely well-regulated process that ensures the maintenance of a balance between fluid gain and loss through different physiological mechanisms such as neural regulation of thirst, hormonal regulation (vasopressin and natriuretic peptides), management through the skin, hemodynamic changes, and renal control of salt and water excretion. In particular, renal excretion of urine also ensures the elimination of products of metabolic activity and excess electrolytes in addition to water, thus maintaining fluid homeostasis. Fluid balance so inextricably links with electrolyte balance both in the intracellular (rich in K^+ ions) and extracellular (rich in Na^+ & Cl^- ions) compartments, that unsurprisingly, trading of electrolytes is the core strategy of renal fluid regulation. Drugs that affect renal regulation of electrolyte excretion have the greatest effect in terms of the quantity of fluid control and thus water homeostasis.[1][2][3]

Diuretics are drugs that pharmacologically tilt the renal fluid regulation in favor of the excretion of water and electrolytes. Thus, diuretics are substances that increase the production and volume of urine. This class of drugs achieves this objective primarily by suppressing receptors that aid in the reabsorption of Na^+, the most abundant extracellular cation, from the renal tubules, thereby increasing the osmolality of the renal tubules and consequently suppressing water reabsorption. Osmotic diuretics cause a direct increase in luminal hyperosmolarity in the renal tubules without affecting electrolyte balance, whereas aquaretics are substances that act directly by only affecting the excretion of water.[4][5]

Diuretics fall into several classes and subcategories depending on their mechanism and site of their action along the nephron. which lists all the available individual drugs in all the different classes, their peculiarities, chemical nature, their major site of action along the nephron, diuretic target molecule, and the percentage of Na+ reabsorption blocked.[6][7][8] Additionally, also gives information (to put things in a broader perspective) about miscellaneous agents that do not have a conspicuous diuretic action and are not used for diuresis, but they do have some diuretic effect which is noticeable which must be taken into account during therapy with these agents.

1. Decreased renal perfusion leading to activation of the renin-angiotensin-aldosterone-system (RAAS) and

2. Long-standing venous stasis leading to extravasation of fluid into the interstitial space, both of which lead to intravascular volume expansion and result in signs of congestion such as weight gain, dyspnea, and generalized edema.[9]

The addition of thiazide diuretics (metolazone, hydrochlorothiazide) to loop diuretics can help relieve symptoms when loop diuretics are not sufficient in HF, as detailed below in the administration section. Aldosterone receptor antagonists (ARA) reduce the mortality and morbidity of advanced systolic HF and patients with ejection fraction less than 35% falling into NYHA-HF classification categories II-IV. This effect is because aldosterone escapes suppression on chronic use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), whereas the addition of ARAs can protect from the effects of aldosterone in such patients.[10][11][12]

Diuretics, along with salt restriction, are also recommended as the first-line therapy in ascites due to liver cirrhosis.[13] In cirrhotic ascites, spironolactone is the drug of choice for initial therapy (due to its antiandrogenic effect), although a loop diuretic may be added as an adjunct if the treatment fails or can be added at the outset in synergistic combination therapy.[14][15] In both HF and cirrhosis, renal dysfunction contributes to the pathophysiology through further activation of RAAS to increase fluid retention.[16][17] Fluid overload that develops in renal insufficiency or acute kidney injury patients increases mortality, and loop diuretics are the favored initial therapy in these patients though renal replacement therapy is the long-term solution.[18][19] Nephrotic syndrome (NS), characterized by hypoalbuminemia, proteinuria, and hyperlipidemia, is an edematous condition that requires diuretic therapy.[18] Activation of epithelial Na+ channels (ENaCs) in the collecting ducts is the mechanism of edema formation in NS, while RAAS activation could also play a minor role. All the diuretics are serum albumin-bound, and hence hypoalbuminemia in NS decreases the load of diuretic delivered to the renal tubules. Co-administration of albumin with furosemide or a combination of furosemide and ENaC inhibitor such as triamterene has shown some success in kidney disease patients with hypoalbuminemia.[20][21] A gain-of-function mutation in ENaC receptors clinically causes Liddle syndrome, for which ENaC inhibitor amiloride is the treatment of choice.[22]
The main aim of the study is phytochemical studies and diuretic effect of matricaria chamomilla hydro alcoholic extract

MATERIALS AND METHODS

Plant Collection
Fresh herbal plant materials were collected from hills of anatagiri forest. The collected plants material (dried flowers) were air-dried in darkness at room temperature (20ºC+/-2ºC). The dried plant material was cut up and stored in tightly sealed dark containers until needed.

Extraction of plants
Dried plant material approximately 5 grams was coarsely crushed in small pieces of 2-5 mm using the cylindrical crusher and extracted with water and ethanol, respectively. Each infusion was prepared using 5 g of dried herbal tea in 200 ml of distilled water and (equivalent to 1 tea cup) at approximately 100ºC+/-1ºC for 10 min. Each aqueous extract was filtered through a paper filter, and stored under refrigeration in glass flasks tapered with screw plastic lid. Both the infusion time and the solvent initial temperature used in this study have been described by several authors as efficient conditions to extract phytochemical compounds, such phenolic and flavonoid compounds from herbs.

Phytochemical Test

Chemical tests performed in the screening and identification of phytochemical constituents in the tested medicinal plants were carried out in extracts as well as powder specimens using the standard procedures.

Experimental animals

The Adult female Swiss mice weighing between (20-30 g) were used to calculate LD50 and female and male wistar rats with an average weight of 180- 220 g were used in sub-chronic toxicity study. They were housed in clean polypropylene cages and maintained under standard conditions of light (12 hours with alternative day/night cycles), relative humidity (60-70%) and temperature (26 ± 1 °C). The animals were fed daily with rodent pellet diet and tap water *ad-libitum* under strict hygienic conditions.

Acute Toxicity Study

Acute oral toxicity study of the *Matricaria chamomilla* L. water extract was performed according to OECD 425 guidelines. Four groups of Adult female Swiss mice (n = 3) were kept fasting for 3- 4 hr and provided only water. One control group treated with the vehicle (distilled water), three groups treated with MCWE at 300 and 2000 mg/kg body weight by gastric intubations. The Rodents were observed for behavioral and neurological symptoms continuously for the first 4 h after dosing. The number of survivors was noted after 24 h and these animals were then maintained for further 14 days with observations made daily. If mortality was observed in two out of three mice, then the dose administered was assigned as toxic dose. If mortality was observed in one mouse, the same dose was repeated again to confirm the toxic dose. No mortality or morbidity was observed in MCWE treated rodents up to 2000 mg/kg. Hence 200 mg/kg and 400 mg/kg doses were taken for efficacy studies.

The animals were kept fasted after a 16-19 hours overnight afterwards, blood samples were collected from each animals by retro-orbital puncture under diethyl ether anesthesia at days intervals 0, 7 and 15.

The blood samples were put in EDTA tubes and used for determining the biochemical parameters and into heparinised tubes for hematological parameters.

Determination of hematological parameters

The blood samples were analyzed for red blood cell (RBC) count, hemoglobin (Hb) levels, hematocrit (HCT), platelets (PLT), White blood cell (WBC) count, differential WBC count [Neutrophils (N), Lymphocytes (L), Monocytes (M), Eosinophils (E)], mean corpuscular volume (MCV), mean corpuscular hemoglobin (MH) and mean corpuscular hemoglobin concentration (MCHC).

Determination of serum biochemical parameters

The blood samples were centrifuged at 4000 rpm for 10 minutes to obtain serum for the following investigations: Alanine amino transferase (ALT), Aspartate amino transferase (AST), Urea, Creatinine, Glucose.

Histopathology

All rats were sacrificed at the end of the study period and subjected to detailed gross necropsy. Vital organs such as heart, kidneys, liver, lung and spleen were isolated from all rats, weighed and examined for any large lesions. All tissues were preserved in 10% buffered formaldehyde solution for histopathological examination. The tissues were embedded in paraffin, and then sectioned, stained with haematoxylin and eosin and were examined microscopically.

Screening for Diuretic Activity

The hydro-ethanolic extract of *Matricaria chamomilla* leaves will be evaluated for its diuretic activity with slight modifications of and other methods. Male wistrar rats will be weighing between 180-200 gms. Divided into 4 groups, (n=6). Animals of group I received distilled water (vehicle) which served as a control. Group II received furosemide 20 mg/kg p.o served as standard. Group III- serve as a low dose aqueous ethanolic extract of *Matricaria chamomilla* of IV- serve as a high dose aqueous ethanolic extract *Matricaria chamomilla* Four animals will be placed in standard metabolic cages.

To be collect the urine samples different time intervals such as 5 & 24 hrs. Observe the parameters such as urine volume, PH, Urinary Na^+, K^+ and Cl^-

Statistical analysis

Experimental results were expressed as mean ± SEM (n=6). Statistical analysis was performed with one way ANOVA followed by Dunnetts test using Graph Pad prism software.

RESULT AND DISCUSSION

Phyochemical Analysis

The phytochemical screening results revealed that the after which it was observed whether the alkaloids were absent due to absence of turbidity and/or precipitate formation. The colour changed from violet to blue or green in some samples indicated the presence of steroids. An interface with a reddish brown coloration was formed in the presence of terpenoids, as positive result. Red coloration identifies thepresence of flavonoids (Shinado's test). A colour change was observed in the test tube, which indicated in the presence of tannins.

Table No: 1: Phyochemical Analysis

S.No	Phytochemicals	*M. chamomilla*
1	Alkaloids	-
2	Steroids	+
3	Terpenoids	+
4	Flavonoids	+
5	Tannins	+

+, Presence of the compound
-, Absence of compound

Acute toxicity

Oral administration of the *Matricaria chamomilla* extract up to dose 2000 mg/kg in mice did not cause any mortality or any toxicity during the experimentation period However, mice after receiving *Matricaria chamomilla* extract exhibited a normal action for all the group of animals, monitored haematological, biochemical, histopatological and also no death was observed. The *Matricaria chamomilla* at 2000mg/kg body weight orally is safe for consumption and for medicinal uses in according with the OECD guidelines No.423. Based on the above study to fixed the dose 200 and 400 mg/ kg for diuretic action.

As per OECD 423 guidelines perform the above dosing to the 3 hours fasted animals to given the special observation for 24 hours to find the grooming sniffing and rearing characteristics for all the groups but other characteristics absent (mortality, excess urination, hair loss, convulsion and locomotion).

Daily observation of food intake was normal for all the groups of animals up to 15 days when compared to standard clinical animal data by the above parameter indicated that the given doses of extract have not induce the diabetes mellitus and pancreas dysfunction related diseases.
Water intake was normal for all the groups of mice up to 15 days when compared to typical scientific

animal data by the above parameter point out that the given drug have not induce the diabetes mellitus, pancreas dysfunction related diseases and other GIT associated diseases

By the observation of daily body weight was no changes for all the groups each mouse when compared to scientific standard data of mouse. Above results of animals body weights of mice have indicated that the given doses of extract are not inducing the obesity and not enhance the cholesterol level. After doses of extract administration no hair loss was found to be each mouse of all the groups, which are expressed not induce the cancer and immunological disorders. Observed parameters have indicated that the no excess urination in all the group of animals so the doses of extract not induce the urinary system related disorders.

Haematological

By the 15 days study indicated that the Table No:2 clarified parameters such as RBC, Haemoglobin, Haematocrit, Platelets WBC, Neutrophils, Lymphocytes, Monocytes, Eosinophils, MCV, MCH and MCHC were normal for after the drug at the day of zero. After the seven days treatment above parameters are not changed when compared to zero day. At the day of 15th milder variations were observed when compared to zero day. In control group comparison indicated that the different days intervals 0, 7 and 15 days above parameters are similar by the indication administered drug not produced any toxic effect.

Biochemical

Biochemical study results expressed that the Table No:3 elucidate parameters such as ASAT (U/I), ALAT (U/I), Urea (mg/l), Creatinine (mg/l), Glucose (g/l) were normal for after the drug at the day of zero. After the seven days treatment above parameters such as glucose, urea and creatinins are not changed when compared to zero day. At the day of 15th milder of biochemical variations were observed when compared to zero day. In control group comparison indicated that the different days intervals 0, 7 and 15 days above parameters are similar by the indication administered drug not produced any toxic effect. After the drug treatment ASAT (U/I) and ALAT (U/I) levels were moderately increased when compared to control group, which indicated extract have antioxidant property.

Histopathology

Various organs histopathology report was revealed that the kidney liver, stomach, heart, spleen, lungs were not cellular changes observed different dose levels 300 & 2000 mg / Kg.

Mortality

In the observation of 15 days mortality rate was zero (Alive percentage -100) by the indication to founded cookies LD_{50} value 2000mg / Kg for 1 in 10th (200 mg / Kg), 1 in 5th (100 mg / Kg) & 1 in 5th (400 mg / Kg) doses , which may used for specific animal model like diabetic and bioavailability studies.

Table No: 2: Hematological values of rats in the Acute toxicity study of Hydro Alcoholic *Extract* of *Matricaria chamomilla*

	0 Day			7th Day		15th Day	
parameters	Normal	300mg/kg	2000mg/kg	300mg/kg	2000mg/kg	300mg/kg	2000mg/kg
RBC	7.89 ± 0.73	7.7 ± 0.60	7.69 ± 0.71	7.66 ± 0.35	8.14 ± 0.64	8.08 ± 0.6	8.38 ± 0.86
Haemoglobin	14.58 ± 0.73	14.55 ± 0.26	14.26 ± 0.31	14.07 ± 0.74	14.25 ± 0.54	14.8 ± 0.64	14.71 ± 0.64
Haematocrit	39.75 ± 0.79	40.08 ± 0.48	40.93 ± 0.65	40.75 ± 0.77	41.65 ± 0.82	42.65 ± 0.93	42.26 ± 0.97

Platelets	623 ± 63	594.00 ± 71	585.00 ± 87	631 ± 63	597 ± 93	599 ± 81	597 ± 91
WBC	10.54. ± 2.1	10.62 ± 0.45	11.13 ± 0.88	11.06 ± 0.8	11.75 ± 0.70	10.83 ± 0.97	11.85 ± 0.45
Neutrophils	20.75 ± 1.89	20.8 ± 0.32	20.62 ± 0.88	21.12 ± 0.2	20.28 ± 0.96	21.17 ± 0.29	20.34 ± 1.08
Lymphocytes	70.51 ± 2.66	70.98 ± 2.06	70.56 ± 2.01	70.81 ± 2.77	69.03 ± 3.07	68.1 ± 3.61	67.91 ± 3.93
Monocytes	2.03 ± 0.17	2.01 ± 0.08	1.98 ± 0.09	2.05 ± 0.18	2.00 ± 0.18	2.00 ± 0.3	2.03 ± 0.33
Eosinophils	1.7 ± 0.43	1.7 ± 0.37	1.7 ± 0.36	1.73 ± 0.34	1.73 ± 0.35	1.75 ± 0.32	1.75 ± 0.34
MCV	51.47 ± 1.25	51.8 ± 0.79	51.7 ± 0.84	51.02 ± 1.65	51.37 ± 0.86	51.92 ± 1.98	51.5 ± 0.84
MCH	18.34 ± 0.69	17.75 ± 0.63	18.15 ± 0.65	17.87 ± 0.66	17.97 ± 0.82	18.46 ± 0.88	18.33 ± 1.82
MCHC	34.17 ± 0.47	34.2 ± 0.36	34.3 ± 0.36	34.03 ± 0.77	34.46 ± 0.88	34.2 ± 0.49	34.01 ± 0.87

Table No: 3: Biochemical values of rats in the chronic toxicity study of Hydro Alcoholic *Extract* of *Matricaria chamomilla*

Treatment Schedule							
	0 Day		**7th Day**			**15th Day**	
parameters	Normal	300mg/kg	2000mg/kg	300mg/kg	2000mg/kg	300mg/kg	2000mg/kg
ASAT (U/I)	84 ± 2.1	85 ± 1.9	83 ± 1.7	83 ± 2.0	85 ± 2.1	84 ± 1.9	85± 2.3
ALAT (U/I)	65.83 ± 4.3	61.33 ± 4.6	65.66 ± 3.65	64.55 ± 4.15	65.16 ± 4.18	66.55 ± 4.11	64.83 ± 3.22
Urea (mg/l)	0.26 ± 0.05	0.26 ± 0.06	0.28 ± 0.03	0.25 ± 0.09	0.26 ± 0.07	0.34 ± 0.04	0.35 ± 0.06
Creatinine (mg/l)	5 ± 0.63	4.73 ± 0.42	4.96 ± 0.27	5.03 ± 0.28	5.11 ± 0.20	4.88 ± 0.49	4.92 ± 0.17
Glucose (g/l)	1.52 ± 0.12	1.02 ± 0.08	1.15 ± 0.11	1.08 ± 0.4	1.11 ± 0.39	1.07 ± 0.45	1.12 ± 0.35

Diuretics action

The results of the evaluations carried out on the extracts are listed Table.No: 4 shows the urinary volume (ml/100g/8h) and electrolyte (Na+ and K+) content (mequiv/100g/8h) of the urine of the animals. Urine volume. Table 1 shows that the reference diuretic, HCTZ, increased urine volume by 54%. The Hydro Alcoholic Extract of *Matricaria chamomilla* also caused an increase in urine volume. For the Hydro Alcoholic *Extract* of *Matricaria chamomilla*, the increase at doses of 200 mg/kg body weight and 400 mg/kg body weight was 18% ($p < 0.01$) and 41 % ($P < 0.001$), respectively, compared to the control group.

Table No: 4: Diuretic effect of Hydro Alcoholic *Extract* of *Matricaria chamomilla* Lipschiz Test Method

S. No	Groups	Total urine Vol (ml/kg BW/5 hrs)	Na+ mmol/L	K+ mmol/L	Cl− mmol/L
1	Control (10 ml/kg BW)	13.22±0.32	107.42±0.75	48.00±0.32	76.99±0.23**
2	Standard (Frusemide 10 mg/kg BW)	21.00±0.03	189.01+0.64	82.03±0.44	128.07±0.24**
4	HA EMC (200 mg/kg BW)	16.41±0.66	165.03±0.63	73.38±0.43	100.46±0.42**
5	HA EMC (400 mg/kg BW)	19.45±0.41	178.93±0.73	81.32±0.35	113.06±0.06**

Statistical analysis done by using Lipschiz Test Method $P < 0.01^*$ $P < 0.001^*$ Significant different from control HA EMC: Hydro Alcoholic *Extract* of *Matricaria chamomilla*,

SUMMARY AND CONCLUSION

While the traditional medicines are derived from medicial plants, minerals and organic matter, the herbal drugs are prepared from medicinal plants only. Use of plants as a source of medicine has been inherited and is an important component of the health care system in India. In the Indian systems of medicine, most practitioners formulate and dispense their own recipes, hence this requires proper documentation and research. The major hindrance in the amalgamation of herbal medicines into modern medical practices is the lack of scientific and 170 clinical data and better understanding of efficacy and safety of the herbal products. Herbs that stimulate the kidneys were traditionally used to reduce edema. In the present investigation one medicinal plants Hydro Alcoholic Extract of *Matricaria Chamomilla* . This current research work will be very beneficial in figuring out the *Matricaria chamomilla* leaves extract diuretic effect by determining the ions and electrolyte excreted by the animals using ion selective channel inhibition. Acute toxicity studies will be performed for the species *Matricaria chamomilla* which may have not shown any toxicity, which human body could be proved with the help of obtained study results. Diurectic activity of the herb *Matricaria chamomilla has* some beneficial effect on the selected animals, the herb *Matricaria chamomilla* may be selected for the further molecular level studies, ***invivo*** and ***invitro*** models are neccssary to get the complet information of the drug Matricaria chamomilla before using the plant in human volunteers.

REFERENCES:

1. Popkin BM, D'Anci KE, Rosenberg IH. Water, hydration, and health. Nutr Rev. 2010 Aug;68(8):439-58. [PMC free article] [PubMed]
2. Roumelioti ME, Glew RH, Khitan ZJ, Rondon-Berrios H, Argyropoulos CP, Malhotra D, Raj DS, Agaba EI, Rohrscheib M, Murata GH, Shapiro JI, Tzamaloukas AH. Fluid balance concepts in medicine: Principles and practice. World J Nephrol. 2018 Jan 06;7(1):1-28. [PMC free article] [PubMed]
3. Jéquier E, Constant F. Water as an essential nutrient: the physiological basis of hydration. Eur J Clin Nutr. 2010 Feb;64(2):115-23. [PubMed]
4. Wile D. Diuretics: a review. Ann Clin Biochem. 2012 Sep;49(Pt 5):419-31. [PubMed]
5.

Donato V, Lacquaniti A, Cernaro V, Lorenzano G, Trimboli D, Buemi A, Lupica R, Buemi M. From water to aquaretics: a legendary route. Cell Physiol Biochem. 2014;33(5):1369-88. [PubMed]
6. Kharod SC, Kang SK, Kadam SD. Off-Label Use of Bumetanide for Brain Disorders: An Overview. Front Neurosci. 2019;13:310. [PMC free article] [PubMed]
7. Huxel C, Raja A, Ollivierre-Lawrence MD. StatPearls [Internet]. StatPearls Publishing; Treasure Island (FL): May 22, 2023. Loop Diuretics. [PubMed]
8. Akbari P, Khorasani-Zadeh A. StatPearls [Internet]. StatPearls Publishing; Treasure Island (FL): Jan 23, 2023. Thiazide Diuretics. [PubMed]
9. Miller WL. Fluid Volume Overload and Congestion in Heart Failure: Time to Reconsider Pathophysiology and How Volume Is Assessed. Circ Heart Fail. 2016 Aug;9(8):e002922. [PubMed]
10. Sica DA, Gehr TWB, Frishman WH. Use of Diuretics in the Treatment of Heart Failure in Older Adults. Heart Fail Clin. 2017 Jul;13(3):503-512. [PubMed]
11. Mullens W, Damman K, Harjola VP, Mebazaa A, Brunner-La Rocca HP, Martens P, Testani JM, Tang WHW, Orso F, Rossignol P, Metra M, Filippatos G, Seferovic PM, Ruschitzka F, Coats AJ. The use of diuretics in heart failure with congestion - a position statement from the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2019 Feb;21(2):137-155. [PubMed]
12. Shah A, Gandhi D, Srivastava S, Shah KJ, Mansukhani R. Heart Failure: A Class Review of Pharmacotherapy. P T. 2017 Jul;42(7):464-472. [PMC free article] [PubMed]
13. Haberl J, Zollner G, Fickert P, Stadlbauer V. To salt or not to salt?-That is the question in cirrhosis. Liver Int. 2018 Jul;38(7):1148-1159. [PubMed]
14. Moore KP, Aithal GP. Guidelines on the management of ascites in cirrhosis. Gut. 2006 Oct;55 Suppl 6(Suppl 6):vi1-12. [PMC free article] [PubMed]
15. Garbuzenko DV, Arefyev NO. Current approaches to the management of patients with cirrhotic ascites. World J Gastroenterol. 2019 Jul 28;25(28):3738-3752. [PMC free article] [PubMed]
16. Udani SM, Koyner JL. The effects of heart failure on renal function. Cardiol Clin. 2010 Aug;28(3):453-65. [PMC free article] [PubMed]
17. Hartleb M, Gutkowski K. Kidneys in chronic liver diseases. World J Gastroenterol. 2012 Jun 28;18(24):3035-49. [PMC free article] [PubMed]
18. Sica DA. Diuretic use in renal disease. Nat Rev Nephrol. 2011 Dec 20;8(2):100-9. [PubMed]
19. Khan YH, Sarriff A, Adnan AS, Khan AH, Mallhi TH. Chronic Kidney Disease, Fluid Overload and Diuretics: A Complicated Triangle. PLoS One. 2016;11(7):e0159335. [PMC free article] [PubMed]
20. Gupta S, Pepper RJ, Ashman N, Walsh SB. Nephrotic Syndrome: Oedema Formation and Its Treatment With Diuretics. Front Physiol. 2018;9:1868. [PMC free article] [PubMed]
21. Kitsios GD, Mascari P, Ettunsi R, Gray AW. Co-administration of furosemide with albumin for overcoming diuretic resistance in patients with hypoalbuminemia: a meta-analysis. J Crit Care. 2014 Apr;29(2):253-9. [PubMed]
22. Mubarik A, Anastasopoulou C, Riahi S, Aeddula NR. StatPearls [Internet]. StatPearls Publishing; Treasure Island (FL): Oct 3, 2022. Liddle Syndrome. [PubMed]