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The Pharmacological Effects and the Diuretic Action of Polyporus

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SUMMARY

The diuretic action of Polyporus

"Saline saturated method" was employed to study the diuretic effects of polyporus. The concentration and urine flow rate of sodium, potassium, and chloride were determined and also the pH effects were measured. The results showed that polyporus is an effective diuretic agent, and within 30 minutes injection of the polyporus extraction, the sodium concentrations of urine flow increased more than 50% and it had the same effect over chloride concentration, the concentration of potassium, showed little or no change and pH of urine was stable.

Each of the following diuretic agents; mannitol, acetazolamide, furosemide, ethacrynic acid, thiazide and spironolactone; acts on different sections of the renal tubules. The diuretic effects of each agent were also evaluated with the same method.

The data indicated the diuretic mechanism of polyporus is very similar to ethacrynic acid. Ethacrynic acid inhibits the active transport of chloride at ascending loop of Henle thus blocking the sodium reabsorption. This process inhibits the urinary concentration mechanism and subsequently causes diuresis. It seems that polyporus may act on ascending loop of Henle in the same fashion and causes diuresis.

INTRODUCTION

Polyporus is the major component of the ancient Chinese herb medicine "oryeongsan". It is reputed to have diuretic action and an anti-hypertensive effect[1-4]. The herb medicine has been used to treat renal diseases and edema in China for thousands of years[5,6]. It is important to understand the nature of the diuretic effect of this drug, particularly, the mechanism of the action of the major ingredients[7,8]. Our study is mainly concerned about the mechanism of diuretic action and side effects of polyporus.

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The method used was to compare the effects of polyorus against well established diuretic agents such as mannitol, acetazolamide, furosemide, ethacrynic acid, thiazides and spironolactone. Each diuretic agent acts with different nature of mechanism[9-16]. The comparison can lead us to understand the function of polyporus as a diuretic agent. Furthermore, it can provide a scientific basis for the pharmacological use of polyporus and oryeongsan and provide evidence of safety of the drug.

EXPERIMENTAL PROCEDURE

1. Extracion of Polyporus
   The crude extractions were extracted by organic solvents (acetone). The extracted solute was placed in a colding dryer. The dry ingredients were collected then dissolved in Tween 80, and then diluted in saline solution to the concentration of 1mg/ml and adjusted to the correct pH for experiment.
2. "Saline saturated method"[17]
   The female rats (Long evens) with bodyweights of 200gm were anesthetized, (pentobarbital sodium 40mg/kg i.p.) and the ureter and vena femoralis were inserted with polyethylene tubing. Next the infusion pumps were used to inject saline into the rats through vena fermoralis at the rate of 10ml/hr, and in approximately 2-3 hrs the urine flows were stabilized. Different diuretics were applied to experimental objects and the urine flows were collected every 15 minutes or 30 minutes. The concentration of sodium, potassium and chloride, and pH of urine flows were recorded. The pH was measured by digital pH meter HM-105, sodium and potassium by flame photo meter FLM-3 and chloride by $HgNO_3$ titration method.
3. LD_{50} measurement
   This experimental method was done according to the method of Litchfield and Wilcoxon[18]. It estimates the mortal rate of the animal after 24 hours of the i p. injection of compounds. The animal was a male mouse of ICR strain with a body weight of 20-25g. A group of ten mice were given i.p. injections with different concentrations of polyporus.
4. Heart rate, blood pressure and EKG were evaluted by polygraph with normal procedure. The rats were anesthetized before the experiment.
5. Dosage of the diuretics
   (a) Mannitol: Saline solution was dis solved with 10% of mannitol and then 12ml of final solution was injected to rats within one hour continously.
   (b) The dosages of the diuretics applied to the experimental rats were as follow:
      (1) acetazolamide: 0.2mg/200gm
      (2) furosemide: 1mg/200gm
      (3) ethacrynic acid: 0.15mg/200gm
      (4) thiazide: 1mg/200gm
      (5) spironolactone: 0.2mg/200gm
      (6) polyporus extraction: 0.25mg/200gm
6. Statistical analysis was performed with the paired student's t-test, all values were expressed as mean ± SE.

RESULTS

After an within 30 minutes injection of 0.25ml of 1mg/ml crude extraction of polyporus into the rats (approximate 200g), the urine flow increased 50%, and at the same time sodium and chloride flows also increased 50%, potassium showed 20% increment and the pH was stable. The pharmacological effects diminished within 60 minutes. (Table 7).

The same experimental method was also applied to well established diuretics such as mannitol, acetazolamide, furosemide, ethacrynic acid, thiazide and spironolactone.

The function and result of each diuretic is as follows:

Mannitol: A sugar like mannitol is filtered freely through the glomerulus but not reabsorbed to any significant extent[9]; the impermeable solute thereby inhibits the osmotic reabsorption of water and leads diuresis[13,19]. The diuretic action increases of the urine flow, sodium flow and chloride flow, however, the potassium flow shows very little change and pH increases slightly. (As a result K:Na in the urine also decreased.) (Table 1).

Acetazolamide: Acetazolamide is a carbonic anhydrase inhibitor, The proximal tubule is the principal site of diuretic action[19,20]. The pharmacological effects of acetazolamide is a slow, but long lasting increase of urine flow also an increase of sodium flow[19,13,20], a decrease of potassium and chloride flows, and the pH showed substantial increase. (Table 2).

Furosemide: Furosemide essentially abolishs the urinary concentrating process by acting on the medullary and cortical portion of the ascending thick limb of loop of Henle[9,21,22]. It is the most effective diuretic[12]. Within 30 minutes of injection the urine flow increases twofolds, sodium and chloride flows also increase more than 100%, but potassium shows little change and the pH decreases. This pharmacological effect lasts 90 minutes plus. (Table 3).

Ethacrynic acid: Ethacrynic acid also blocks the urinary concentrating process by inhibiting the chloride active transport at ascending loop of Henle, thus decreases net solute reabsorption and causes diuresis[9,12,13,23,24]. In first 30 minutes of injection, the urine flow increases 50% sodium and chloride flows also show an increase, potassium flow slightly increase and the pH is slightly decrease. (Table 4).

Thiazide: It impairs urinary dilution by acting on distal convoluted tubule to reduce active sodium transport to cause diuresis[10,12,13,24,25]. After 30 minutes of injection urine, sodium, chloride and potassium flows increase 50%, and the pH is stable. (Table 5).

Spironolactone: Spironolactone is a potassium-sparing diuretic causing mild natriuresis while decreasing potassium and hydrogen secretion[13,24,26,27]. It causes increase of urine, sodium and chloride flows within 30 minutes of injection but little change on potassium flow, and the pH is table. The pharmacological action is slow but lasts for more than two hours. (Table 6).

The estimation of LD_{50}: After 24 hrs of an injection of maximum volume; 1 ml of polyporus (10 mg/ml), all of the experimental

Table 1. Effect of Mannitol on Urine Flow, Na^+, K^+, Cl^-, pH Change in Urine of Rats

Time (min)	Urine flow (μl/min)	U.Na.V (μEq/min)	U.K.V. (μEq/min)	U.Cl.V (μEq/min)	pH
Control	159.90±32.98[a] (100)	22.73±4.43 (100)	2.87±0.23 (100)	27.12±4.99 (100)	6.24±0.25 (100)
0-30	413.20±47.79** (258)[b]	46.39±5.45** (204)	3.66±0.26* (128)	43.07±5.94** (196)	6.52±0.15 (105)
30-60	385.40±39.93** (241)	37.73±3.92 (166)	3.32±0.49 (116)	42.05±4.21 (155)	6.71±0.12 (108)
60-90	217.40±24.07 (135)	25.30±2.29 (111)	3.14±0.22 (109)	29.54±2.87 (109)	6.37±0.20 (102)
90-120	140.60±14.81 (88)	21.16±2.40 (93)	2.78±0.20 (97)	24.04±2.38 (89)	6.20±0.24 (99)

a: Mean ± SE. b: Percent change from control data
: Statistically significant compared with control data ($p < 0.05$, **$p < 0.01$)
U: Urine V: Volume
U.Na.V, U.K.V and U.Cl.V denote the excreted amounts of Na^+, K^+, and Cl^- in urine, respecitvely.

Table 2. Effect of Acetazolaminde on Urine Flow, Na^+, K^+, Cl^-, pH Chang in Urine of Rats

Time (min)	Urine flow (μl/min)	U.Na.V (μEq/min)	U.K.V (μEq/min)	U.Cl.V (μEq/min)	pH
Control	87.17±23.68[a] (100)	14.37±3.19 (100)	2.35 ±0.27 (100)	15.95±3.13 (100)	6.03±0.17 (100)
0-30	139.33±10.88* (160)[b]	23.11±1.69** (161)	3.16 ±0.33 (135)	20.53±1.12 (129)	7.81±0.24** (130)
30-60	153.83±17.31* (177)	24.74±2.85** (172)	3.301±0.19* (141)	22.96±2.31* (144)	7.69±0.26** (128)
60-90	159.83±26.50* (183)	24.02±4.17** (167)	3.20 ±0.30* (136)	23.87±4.21* (150)	7.53±0.31** (125)
90-120	139.17±28.97 (160)	21.65±4.38 (151)	2.75 ±0.25 (117)	21.82±4.28 (137)	7.39±0.34** (123)

a: Mean ± SE. b: Percent change from control data
: Statistically significant compared with control data ($p < 0.05$, **$p < 0.01$)
U: Urine V: Volume
U.Na.V, U.K.V and U.Cl,V denote the excreted amounts of Na^+, K^+ and Cl^- in urine, respectively.

Table 3. Effect of Furosemide on Urine Flow, Na^+, K^+, Cl^-, pH Change in Urine of Rats

Time (min)	Urine flow (μl/min)	U.Na.V (μEq/min)	U.K.V (μEq/min)	U.Cl.V (μEq/min)	pH
Control	148.83±17.14[a] (100)	24.84±3.77 (100)	4.15±0.86 (100)	27.65±4.79 (100)	6.23±0.18 (100)
0-30	444.00±30.08** (298)[b]	57.74±3.23** (232)	4.95±0.38 (119)	65.34±4.26** (236)	6.03±0.13
30-60	330.67±20.58** (222)	44.23±2.83* (178)	3.96±0.40 (95)	48.90±2.99* (177)	5.13±0.16**
60-90	234.33±12.33* (157)	33.08±1.74 (133)	3.52±0.22 (85)	36.89±2.11 (133)	4.93±0.16**
90-120	168.50±12.72 (133)	26.95±2.83 (109)	3.62±0.50 (87)	28.96±2.53 (105)	4.92±0.21**

a: Mean ± SE. b: Percent change from control data
*: Statistically significant compared with control data ($*p < 0.05$, $**p < 0.01$)
U: Urine V: Volume
U.Na.V, U.K.V and U.Cl.V denote the excreted amounts of Na^+, K^+ and Cl^- in urine, respectively.

Table 4. Effect of Ethacrynic Acid on Urine Flow, Na^+, K^+, Cl^-, pH Change in Urine of Rats

Time (min)	Urine flow (μl/min)	U Na.V (μEq/min)	U.K.V (μEq/min)	U.Cl.V (μEq/min)	pH
Control	138.83±17.26[a] (100)	19.73±1.11 (100)	2.75±0.22 (100)	21.83±1.50 (100)	6.25±0.26 (100)
0-30	194.00±21.67* (140)[b]	30.09±2.65** (153)	3.29±0.25** (120)	34.99±3.66* (160)	5.96±0.16 (95)
30-60	128.67±14.93 (93)	21.97±3.01 (111)	2.58±0.22 (94)	25.26±3.12 (116)	5.83±0.14 (93)
60-90	124.83±23.06 (90)	18.45±3.49 (94)	2.14±0.41 (88)	20.91±3.63 (96)	5.58±0.16 (89)
90-120	160.33±34.77 (116)	21.24±3.56 (108)	2.41±0.31 (88)	25.01±4.30 (115)	5.39±0.25 (86)

a: Mean ± SE. b: Percentage change from control data
*: Statistically significant compared with control data ($*p < 0.05$, $**p < 0.01$)
U: Urine V: Volume
U.Na.V, U.K.V and U.Cl.V denote the excreted amounts of Na^+, K^+ and Cl^- in urine, respectively.

Table 5. Effect of Thiazide on Urine Flow, Na^+, K^+, Cl^-, pH Change in Urine of Rats

Time (min)	Urine flow (μl/min)	U.Na.V (μEq/min)	U.K.V (μEq/min)	U.Cl.V (μEq/min)	pH
Control	121.11±28.08[a] (100)	19.97±3.29 (100)	3.06±0.42 (100)	24.65±4.44 (100)	6.15±0.23 (100)
0-30	187.11±21.11* (155)[b]	31.42±3.60** (157)	4.30±0.83 (141)	36.22±3.58* (147)	6.60±0.31 (107)
30-60	127.78±17.14 (103)	20.88±2.84 (105)	3.10±0.66 (101)	24.79±3.69 (101)	6.09±0.52 (99)
60-90	124.29±18.81 (103)	18.85±5.92 (94)	2.51±0.63 (82)	21.96±1.97 (89)	5.88±0.54 (96)
90-120	105.77± 8.59 (87)	17.58±1.00 (88)	2.50±0.50 (82)	20.21±0.97 (82)	5.87±0.54 (95)

a: Mean ± SE. b: Percent change from control data
: Statistically significant compared with control data ($p < 0.05$, **$p < 0.01$)
U: Urine V: Volume
U.Na.V, U.K.V and U.Cl.V denote the excreted amounts of Na^+, K^+ and Cl^- in urine, respectively.

Table 6. Effect of Sprionolactone on Urine Flow, Na^+, K^+, Cl^-, pH Change in Urine of Rats

Time (min)	Urine flow (μl/min)	U.Na.V (μEq/min)	U.K.V (μEq/min)	U.Cl.V (μEq/min)	pH
Control	121.86±20.11[a] (100)	18.42±2.28 (100)	2.24±0.31 (100)	19.93±2.56 (100)	6.49±0.22 (100)
0-30	201.57±30.05* (165)[b]	29.97±4.15** (163)	2.87±0.35* (128)	32.99±4.77* (166)	7.27±0.15 (112)
30-60	157.29±24.23* (129)	25.90±3.36** (141)	2.50±0.25 (112)	28.91±3.89* (145)	6.93±0.14 (107)
60-90	165.29±18.20* (136)	25.42±2.70 (138)	2.53±0.13 (113)	28.91±2.55 (145)	6.86±0.13 (106)
90-120	157.57±18.97 (129)	24.35±2.87 (132)	2.48±0.22 (111)	27.37±3.01* (137)	6.61±0.20 (102)

a: Mean ± SE. b: Percent change from control data
: Statistically significant compared with control data ($p < 0.05$, **$p < 0.01$)
U: Urine V: Volume
U.Na.V, U.K.V and U.Cl.V denote the excreted amounts of Na^+, K^+ and Cl^- in urine, respectively.

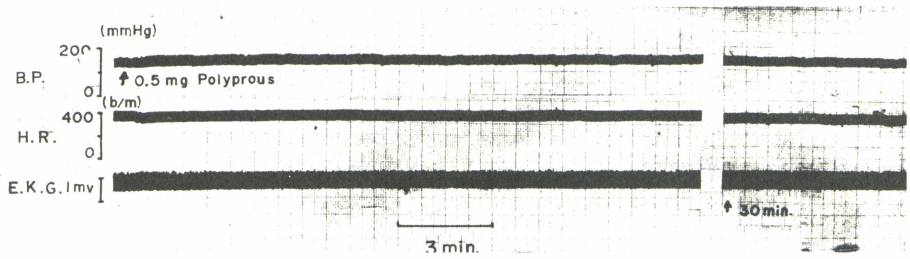

Fig. 1. The effect of polyporus on blood pressure heart rate, and EKG. The figure shows polygraphic records of polyporus extraction i.v. injection. (The dose is 0.5 mg/g).

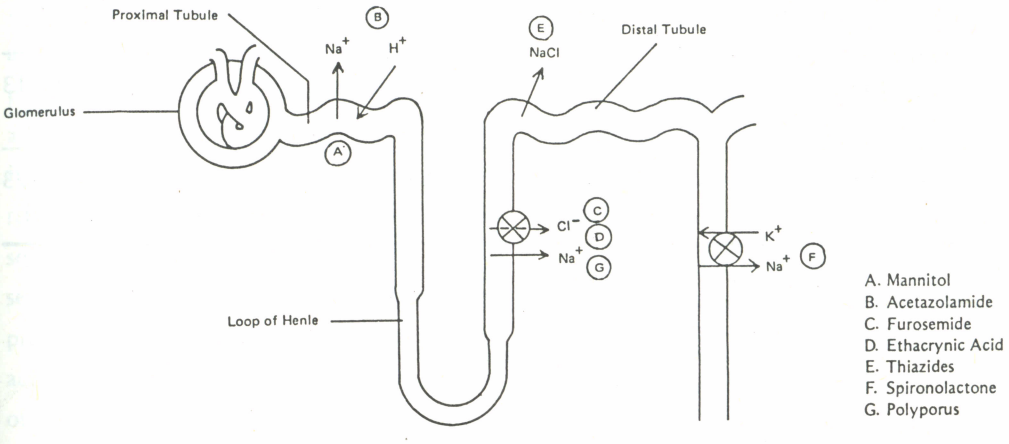

Fig. 2. The actions of diuretics and polyporus on renal tubules.

mice are still alive. Since the mortal rate is zero, we can conclude that LD_{50} for polyporus is larger than 0.4g/mg. The statistical significance of LD_{50} can not be evaluated by this method.

The heart rate, blood pressure and EKG show little change by injection of polyperus. (Figure 1).

DISCUSSION

In general, different diuretics inhibit transport processes in the renal tubules to increase urinary excretion of salt and water is a remarkable feature of this group of drugs[9,12,13,14,15]. Fundamentally, diuretics work by inhibiting solute reabsorption by the tubular epithelial cells. Since the solute and water transport are intimately linked, the inhibition of solute reabsorption constrains osmotic water reabsorption, and diuresis ensues. (Figure 2). Our studies are based on the examination of urination activities such as urine flow rate, urinary sodium, chloride and potassium flow rates and concentration, and sodium vs potassium concentration ratio. Since different diuretics act on different sections of renal tubules with different mechanism of actions, the urination activity can provide the informations regarding the different nature of diuretics[12,13,14,15] (Table 8). The urine flow

Table 7. Effect of Polypous on Urine Flow, Na^+, K^+, Cl^-, pH Change in Urine of Rats

Time (min)	Urine flow (μl/min)	U.Na.V (μEq/min)	U.K.V (μEq/min)	U.Cl.V (μEq/min)	pH
Control	154.00[a]±25.11 (100)	22.90±3.15 (100)	2.97±0.24 (100)	26.22±3.89 (100)	6.19±0.31 (100)
0-30	227.17 ±18.76* (148)[b]	34.75±2.80* (152)	3.53±0.36 (119)	39.59±3.15* (151)	6.16±0.20 (99.5)
30-60	171.17 ±17.39 (111)	26.67±2.04 (117)	3.24±0.27 (109)	30.85±2.27 (118)	5.86±0.26 (95)
60-90	156.17 ±28.17 (101)	24.57±3.53 (107)	3.27±0.39 (110)	28.36±3.80 (108)	5.62±0.13 (91)
90-120	161.00 ±36.94 (105)	23.37±39.5 (102)	2.91±0.25 (98)	27.19±4.44 (104)	5.69±0.23 (92)

a: Mean ± SE. b: Percent change from control data
*: Statistically significant compared with control data ($*p < 0.05$, $**p < 0.01$)
U: Urine V: Volume
U.Na.V, U.K.V and U.Cl.V denote the excreted amounts of Na^+, K^+ and CL^- in urine, respectively.

Table 8. The Pharmacological Action of Major Diuretics in First 30 Minutes of Action

	Urine flow ratio	UNa.V ratio	UK.V ratio	UCl.V ratio	K; Na	CNa (meq/1)	CK (meq/1)	CCl (meq/1)
Mannitol	2.58	2.04	1.28	1.96	1:1.59	142	38.85	128.4
Acetazolamide	1.6	1.61	1.35	1.29	1:1.19	165.9	22.68	147.35
Furosemide	2.98	2.32	1.19	2.36	1:1.95	130	11.15	147.16
Ethacrynic acid	1.40	1.53	1.20	1.6	1:1.28	155	16.96	180.4
Thiazide	1.55	1.57	1.41	1.47	1:1.11	167.92	22.98	193.58
Spironolactone	1.65	1.63	1.28	1.66	1:1.27	148.68	14.24	163.67
Polyporus	1.48	1.52	1.19	1.51	1:1.28	152.97	15.54	174.27

The table estimated by assume control figure 1.00 in comparison to the ratio of the effect of each diuretics after 30 minute injection, except CNa, CCl is the figure of concentration sodium, potassium and chloride respectively.

rate indicated polyporus is different from mannitol and furosemide which are much more effective in the increase of urinary flow (Table 8). Urinary sodium flow shows polyporus is in the same range with acetazolamide, ethacrynic acid, thaizide and spironolactone. Acetazolamide is carbonic anhydrase inhibitors which increases urinary flow in a slow path long-acting effect[19,20]. Spironolactone is a potassium-sparing agent[24,26,27], in the first 30 minutes of injection its urinary activities are quite similar to those of polyporus, however, it is a steroid analogue of a mineralo-corticoid hormone[26-29]. As such, it works through competitive binding to the receptor site where aldosterone influence sodium potassium exchange[27-29]. Consequently, it acts only when aldosterone is present. The result shows it is much longer acting compared to polyprus. Thus the action of polyporus is unlikely to be the same mechanism as spironolactone. In comparing to the duration of pharmacological action, urine flow, sodium, chloride and potassium flow and the pH from the above results, it appears that the effects of the polyporus are very similar to those of ethacrynic acid and thiazide. Ethacrynic acid and thiazide acts on the ascending loop of Henle and distal convoluted tubules respectively[9,10,12,13,23,24,25]. Ethacrynic acid inhibits the urine concentration process, meanwhile, thiazide reduces active sodium reabsorption and blocks urine dilution capacity. If we assume the urine concentration ratio of K:Na is 1 in control experiment,the data shows the change of ratio for thiazide is 1.11, for ethacrynic acid is 0.78, and for polyporus is 0.78 also. The difference indicated thiazide effectively decreases potassium reabsorption, and on the contrary, ethacrynic acid and polyporus show little effect on the potassium. Basically, thiazide impairs the urinary dilution by acting on distal convoluted tubule to reduce active sodium transport and causes diuresis, however, in the distal convoluted tubule, sodium exchange may influence potassium activity but not in the loop of Henle[10,12,25,30,31]. From above discussion and observation of urinary activities, it appears that without effect over potassium reabsorption the action of polyporus is very similar to ethacrynic acid. This may lead to the conclusion that the most probable acting site of polyporus is at the ascending loop of Henle. The major functions of ethacrynic acid are inhibits the active chloride transport, reduces sodium transport and abolishs the urinary concentrating process[23,24,32]. The urinary activity indicated polyporus may also act on renal tubule with the same mechanism.

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豬苓之藥理及利尿作用

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摘　要

本研究以膀胱導尿法研究豬苓的利尿作用及機轉，大花鼠的排尿速率，鈉離子，鉀離子和氯離子的濃度都被測定，而尿的酸性也被測定。由實驗數據顯示豬苓是十分有效的利尿劑，我們以豬苓的初抽取液注射大花鼠在30分鐘內，尿中的鈉離子增加百分之五十的速率排出，豬苓對氯離子也有相等作用，鉀離子排出無顯著的改變，而尿中酸度也呈穩定狀態。對腎小管的作用部位以機轉已知的常用利尿劑有Mannitol，Acetazolamide，Furosemide，Ethacrynic acid，Thiazide，Spironolactone 的利尿作用也用相同方法測定，然後比較豬苓的作用，實驗結果顯示豬苓的利尿作用及機轉十分近似Ethacrynic acid，此利尿劑抑制上行亨利氏管內氯離子的輸送進而減少或完全停止鈉離子的再吸收，這個作用會抑制尿的濃縮作用進而引起利尿作用，我們基本結論是豬苓也是作用上行亨利氏管而與利尿劑Ethacrynic acid相同作用的機轉而引致利尿。

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