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Lemon fruits lower the blood uric acid levels in humans and mice

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ABSTRACT

Hyperuricemia is a chronic metabolic disorder leading to gouty arthritis, kidney stones, hypertension, renal failure and even cardiovascular diseases in humans. In the present study, the role of the lemon fruit juice and/or the water soluble extracts in lowering the blood uric acid level was evaluated in both human subjects and mice. Fresh lemon fruits, excluding the peel and seeds, were used to prepare the juice and/or water soluble extracts. Human subjects with hyperuricemia were given the freshly squeezed pure lemon fruit juice daily at 30 mL/day (equivalent to a lemon a day) for 6 weeks. Human serum samples were collected for biochemical assessments at weeks 0 (basal line), 3, and 6, respectively. At the end of clinical study, fasting blood samples were collected for blood tests. Mice were given oxonic acid potassium (OA) to induce hyperuricemia. Hyperuricemic Mice were orally given the lemon fruit water soluble extracts at 10 mg/kg body weight and/or allopurinol at 5 mg/body weight for 11 consecutive days. At the end of study, the mice were euthanized and the blood and liver tissues were collected for biochemical tests. The results showed that the lemon fruit juice and/or the water soluble extracts significantly lowered serum uric acid levels in both human subjects and mice. Neither renal nor liver dysfunction was observed. The mechanistic results indicated that lemon might exert the role in lowering serum uric acid independent of inhibition of xanthine oxidase. The results lay a foundation for the future development of dietary treatments of hyperuricemia in humans.

1. Introduction

Hyperuricemia is a metabolic disease as presented by elevation of the blood uric acid level. Uric acid is the end product of purine metabolism in humans. A blood uric acid level, e.g., urate greater than 360 mmol/L (6 mg/dL) for women and 400 μmol/L (6.8 mg/dL) for men, is the diagnosis for hyperuricemia. The occurrence of hyperuricemia is related to a variety of factors, such as lifestyle, nutrition balance, medication, gender, age, and genetics (Musacchio et al., 2016). Imbalanced nutrition and increased consumption of alcohol leads to the increased prevalence of the disease in certain populations, particularly in that of young adults (Zhou and Liu, 2015). The prolonged on-set of hyperuricemia is associated with the development of hypertension, hyperlipidemia, hyperglycemia, gouty arthritis, kidney stones, renal failure, and cardiovascular diseases (Becker et al., 2005; Dehghan et al., 2008; Kang and Nakagawa, 2005; Krishnan et al., 2011; Mazzali et al., 2001; Tatsuno and Saito, 2001). According to the 2004 National Survey, conducted by the China National Research Center for Disease and Health, there are more than 120 million hyperuricemic cases reported in China. Therefore, there is an urgent need to develop a strategy to treat and prevent hyperuricemia.

Therapeutic drugs for hyperuricemia are now available, such as allopurinol and benzbromarone (Tung et al., 2015). These drugs are synthetic and often related to adverse side effects (Becker et al., 2005; Stamp and Jordan, 2011). For instance, allopurinol is associated with the increased, potential risk of rash, fever, renal, liver and kidney diseases (Haidari et al., 2009). Benzbromarone has the capability of causing fulminant hepatotoxicity (Yu et al., 2006). Therefore, natural fruits and vegetables, and their bioactive compounds as potential alternatives, have recently received considerable attention in the treatment of hyperuricemia.

Lemon fruits are rich in bioactive compounds such as vitamin C, citric acid, hesperidin, sodium, and potassium. Previous publications have reported that lemon and orange juice can be used to treat hyperuricemia urinary calculus (Aras et al., 2008), calcium oxalate calculus (Kulaksizoglu and Sofikerim, 2008), and kidney calculus (Touhami et al., 2007). However, it remains unclear whether lemon fruits lower the blood uric acid level in mammals. Therefore, the aim of the current study was to determine the role of lemon

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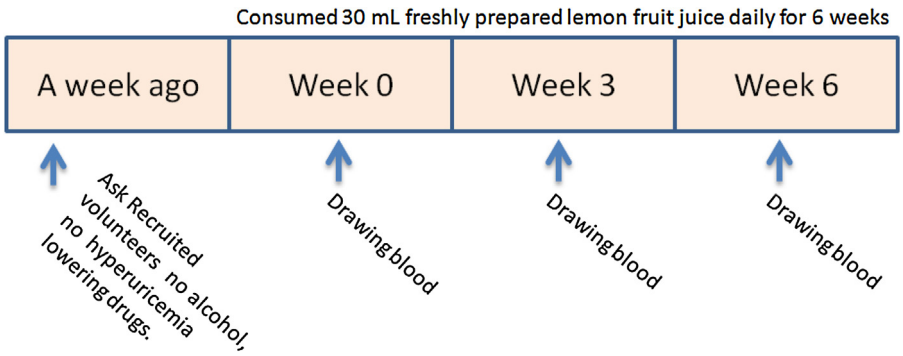

Fig. 1. Clinical trial workflow.

Table 1
Basic information and serum uric acid level regarding subjects (volunteers).

Volunteers	Sex	Age	Gout	Previous urate-lowering therapy	UA content (umol/L)		
					Week 0	Week 3	Week 6
1	M	35	N	Y	642	646	508
2	M	28	N	Y	628	745	658
3	M	29	Y	Y	522	642	454
4	M	37	N	N	500	431	354
5	M	50	N	N	533	491	594
6	M	32	N	N	592	648	624
7	M	22	N	Y	538	575	664
8	M	31	Y	N	538	314	End
9	M	33	N	N	702	614	567
10	M	37	N	N	643	713	547
11	M	39	N	N	455	Discontinued	
12	M	27	Y	Y	814	Discontinued	
13	M	45	N	N	603	Discontinued	
14	M	50	N	N	471	Discontinued	

M: man; Y: yes; N: no.

fruit juice and bioactive water soluble extracts in the treatment of hyperuricemia in human subjects and mice.

2. Materials and methods

2.1. Lemon, lemon fruit juice and the water soluble extracts

A large batch of fresh lemon fruits were purchased from the Ruili Experimental Station in the Industrial Crops Institute at Yunnan Academy of Agricultural Sciences, China. The fruits were transferred in a temperature controlled container and stored in the research laboratory at Huazhong Agricultural University in Wuhan, China. For the human lemon intervention study, the lemon fruit juice was freshly squeezed on a daily basis from lemon fruits, after removal of the peel and seeds. Individual subjects were given 30 mL pure lemon juice with no other additional ingredients (equivalent to the amount of a lemon per day). For the animal study, 6000 g lemon fruits were used and the peel and seeds were removed. The freshly squeezed juice (about 1400 mL) was filtered through three layers of cheesecloth to remove the cell debris and other large particles; then, the supernatant was freeze dried, which yielded 64.5 g of freeze dried powder of the lemon fruit juice. The powder was reconstituted in 645 mL distilled water. The clear supernatant solution was used as the lemon water soluble extract (LET) for the animal study.

2.2. Reagent and instrument

Oxygen oxazine acid potassium was purchased from Sigma Chemical Co. (St. Louis, MO, USA). Allopurinol tablets were purchased from China WTO Tianjie Pharmacy (Jiangsu) Co., Ltd. (Nanjing, China). The xanthine oxidase assay kit and coomassie blue staining assay kit were obtained from Nanjing Jiancheng Bioengineering Institute (Nanjing, China). The automatic biochemical analyzer was manufactured by the Siemens Medical Diagnostic Products (Shanghai) co., Ltd. (Shanghai, China).

2.3. Clinical trial

Fourteen patients with hyperuricemia, between the age range of 20 and 55, were recruited for the study. Exclusion criteria include: hyperuricemia induced by blood disease, tumor radiotherapy/chemotherapy or related drugs; heart, cerebrovascular, liver, kidney and hematopoietic system and psychosis; medication for lowering uric acid; participation in other clinical trials; not recommended to consume lemon (those with gastric ulcer, gastric hyperchlorhydria, dental caries and diabetes); and/or other reasons not suitable for clinical trial studies. The subjects consumed 30 mL freshly prepared lemon fruit juice daily for 6 weeks (equivalent to a lemon per day), without any other dietary restrictions, except alcohol and hyperuricemia lowering drugs. During the experimental period, overnight fasting blood samples were collected at weeks 0 (basal line), 3, and 6 (see the trial work flow diagram in Fig. 1). Then the collected blood samples were subject to blood biochemical tests in the affiliated hospital at Huazhong Agricultural University. The work described herein has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. This study has been approved by the ethics committee of Huazhong Agricultural University (Ethical number HZAUHU-2016-005).