# Effect of Ginkgo biloba as Add-on Therapy on Serum Uric Acid in Hypertensive Patients on Valsartan Mono-therapy

*Luma M. Saadallah ; **Imad A-J Thanoon

M.B.Ch.,B; M.Sc; Ph.D (Pharmacology)

*Department of clinical pharmacy, College of Pharmacy, University of Mosul.

**Prof. Dr, Department of pharmacology, College of Medicine, University of Mosul.

Corresponding author Mobile: 07702059103, Email: Lumaalobaidy@yahoo.com

## ABSTRACT:

**Aim:** The study was conducted to evaluate the effect of Ginkgo biloba on serum uric acid level when used as add-on therapy to valsartan in hypertensive patients.

## Patients and Methods:

The study was conducted in Private Clinics in Mosul City-Iraq, during a period of sixth months from 15 October 2017 to15 April 2018. The total number of patients enrolled in the study was 50 hypertensive patients using Valsartan mono-therapy of both sexes. The patients were administered Ginkgo biloba 80 mg twice daily and followed for 2 months duration. Their serum uric acid level was determined at baseline level and after 2 months from administration of Ginkgo biloba.

**Results:** There was a significant reduction on serum uric acid level after two months from addition of Ginkgo biloba.

**Conclusions:** This study revealed that Ginkgo biloba could be regarded as natural and relatively safe drug in reducing serum uric acid level.

**Key words**: Ginkgo biloba, add-on therapy, valsatan monotherapy, hypertensive patients, serum uric acid.

# Introduction:

Ginkgo biloba is one of the most ancient living tree species often referred as a living fossil [(1)]. It has been cultivated in China for several thousand years, then transported to many countries around the world[(2)] . A German surgeon, Englbert Kaempfer, was the first who used the term “Ginkgo” in 1712, but it was Linnaeus who termed it Ginkgo biloba in 1771 [(3)]. Ginkgo was derived from the Chinese world Yinkus, which means “Silver apricot”, biloba referring to its two lobed, fan shaped leaves[(4)].

The Ginkgo leaf contains many active ingredients including polyphenolic flavonoids and terpenoids[(5)]

Ginkgo leaves extract has shown beneficial effect in treating impairments in memory, Alzheimer's, dementia, edema, inflammation, and vaso-occlusive disorders[(6)].

Ginkgo leaf extract appears to be safe to use. It can cause some minor side effects such as, stomach upset, headache, dizziness, constipation, palpitation and allergic skin reactions[(7)].

Uric acid is the end product of exogenous and endogenous purine metabolism[(8)]. The exogenous source of purines varies significantly with diet, while the main sources of endogenous uric acid are the liver, intestine, muscles, kidneys and the vascular endothelium[(9)]. Hyperuricemia contributes significantly to the development of hypertension and coronary heart disease[(10)]. High uric acid levels have been associated with decreased renal perfusion and decreased tubular secretion of uric acid, which may lead to activation of the intrarenal renin–angiotensin system, and then to subsequent elevation of blood pressure[(11)].

At present, non-steroidal anti-inflammatory drugs, corticosteroids, and urate-lowering drugs are often used for treatment of hyperuricemia[(12)]. However these drugs have toxic effect to renal and gastrointestinal systems[(13)]. Thus in the recent years, the need for new and natural sources for treatment of hyperuricemia is increased[(12)], therefore and on this base, this study has been conducted.

## Subjects, Materials and Method:

This study had been conducted over a period of 6 months from 15 October, 2017 to 15 April, 2018 in Private Clinics in Mosul City. The ethical requirement for the study was obtained from the College of Pharmacy in Mosul University and a consent form was obtained from each patient.

Descriptive, A prospective case series study design was used in this six months study. Single group of 58 hypertensive patients on valsartan mono-therapy were participated in the study, only fifty patients completed this study, 8 patients refused to complete this study due to different causes. The dose range of valsartan was between 80mg and 160 mg once daily. Serum uric acid was obtained initially at baseline level and after two months from addition of Ginkgo biloba (provided by Adrein Gagnon, Canada) in a dose of 80 mg twice daily as add-on therapy to valsartan. Inclusion criteria include: Hypertensive patients with duration of the disease for at least 1 year, the patients use only valsartan 80mg or 160 mg for at least 6 months for treatment of hypertension, patients are ≥18 years old. Patients who have diabetes mellitus, epilepsy, renal or liver diseases, pregnant or breast feeding mothers, or patients who used any drug that might affect the coagulation system or drugs other than Valsartan for hypertension were excluded from the study.

Anthropometric measurement were recorded including height (cm) and weight (kg) and body mass index (BMI) was calculated as:

BMI($kg/m^2$)=Weight (kg)/ Height($m^2$) [14] .

Uric Acid was determined by enzymatic spectrophotometric method[15] using a kit provided by Biolabo (France).

Serum uric acid concentration was determined according the following equation:

$$\text{Uric acid concentration} = \frac{absorbance\ of\ sample}{absorbance\ of\ standard} \times n\ (mg/dl)$$

n=concentration of standard= 10 (mg/dl).

The reference ranges of serum uric acid are between 2.6 and 7.2 mg/dl[16].

# Results:

## 3.1 Personal and anthropometric characteristics of the study sampled population:

Fifty patients (23 maleand 27 female), were participated in the study figure (3.1), the age range of the selected group were between 24 and 72 years old (mean 48.2±10.73). The BMI of 26% were below 25 and 74% were above 25 (mean 28.88±5.87) table (3.1).

Regarding dose of valsartan, 28 of hypertensive patients in the study sampled taking 80 mg / day (56.0%), and the other 22 patients receiving 160 mg / day (44.0%) as prescribed by their physicians.

**Table (3.1): Personal and anthropometric characteristics of the study sampled population at the beginning of the study, (n = 50).**

| Characteristics | Mean | SD | Minimum | Maximum |
|---|---|---|---|---|
| **Age (years)** | 48.20 | 10.73 | 24.0 | 72.0 |
| **Height (Cm)** | 165.31 | 8.79 | 150.0 | 187.0 |
| **Weight (kg)** | 78.20 | 12.48 | 50.0 | 110.0 |
| **BMI ($kg/m^2$)** | 28.88 | 5.87 | 19.03 | 44.44 |

### 3.2 The mean uric acid level of the study sampled population at the baseline level:

The mean value of serum uric acid of patients before receiving Ginkgo biloba is shown in table (3.2).

**Table (3.2) : The mean value of serum uric acid of patients at the beginning of study (n=50) .**

| Parameters | Mean | SD | Minimum | Maximum |
|---|---|---|---|---|
| **Uric acid (mg/dl)** | 4.65 | 0.95 | 2.70 | 6.50 |

The results are expressed as mean and SD.

### 3.3 Effect of GB on serum uric acid:

There was a significant reduction in serum uric acid levels after using Ginkgo biloba as add-on therapy to valsartan table (3.3).

**Table (3.3): Changes in serum uric acid after 2 months of "GB usage" in the study sampled patients, (n = 50).**

| Parameters | Base line<br>Mean ± SD | After 2 months<br>Mean ± SD | P-value* |
|---|---|---|---|
| **Uric acid (mg/dl)** | 4.65 ± 0.95 | 4.15 ± 1.30 | **0.001** |

* Paired T-test of two means was used.

## Discussion:

Several studies suggest multiple mechanisms of the beneficial effects of Ginkgo biloba through its antioxidant, antiplatelet, antithrombotic, and vasodilatory properties[17].

In this study Ginkgo biloba caused a significant reduction in uric acid level after two months from treatment, to our knowledge this was the first study that deals with the effect of GB on serum uric acid level in human.

A study done by Elatrash and Abd El-Haleim [18] administered monosodium glutamate (MSG) to rats to cause liver and renal toxicity. Significant elevation of serum uric acid level produced by the effect of MSG, then Ginkgo biloba was added and caused a significant reduction in uric acid levels.

Another study which emphasized our results was that done by Chen *et al* [12].They used rats with acute gout, the pathogenesis of acute gout and the therapeutic effects of Ginkgo biloba extract were investigated by metabolic approach. Twenty-seven potential biomarkers were identified to be involved in tryptophan metabolism, pyrimidine metabolism, pentose phosphate pathway, Tricarboxylic acid cycle, tyrosine metabolism, lysine degradation and purine metabolism, among these biomarker was uric acid, which was the main product of purine metabolism. The therapeutic effect of Ginkgo biloba extract for acute gout with hyperuricemia model rats was evaluated by detecting the degree of metabolic disorder recovery, after treatment with Ginkgo biloba extract, the levels of uric acid and allantoin (a stable biomarker of urate oxidation) were recovered significantly.

The mechanism that might give us a possible explanation about the effect of Ginkgo biloba on uric acid, was xanthine oxidase inhibition effect by flavonoids [19], which was the main active ingredient in Ginkgo biloba [5]. Xanthine oxidase has an important role in the endogenous production of uric acid since it is the key enzyme in the catabolism of purines [8]. These flavonoids rich compounds are structurally similar to xanthine oxidase substrate and so can inhibit the enzyme activity[19].

In conclusion: Ginkgo biloba has smooth, natural and relatively safe effects in reducing serum uric acid level.

## References:


1. Sadaf HM, Bibi Y, Arshad M, Amjad MS. Status of maiden hair tree-ginkgo biloba: living fossils becoming endangered, NJMBS 2014; 3(4): 1-3.
2. Brondino N, De Silvestri A, Re S, Lanati N, Thiemann A, Verna A *et al* . Systematic review and meta-analysis of ginkgo biloba in neuropsychiatric disorders: from ancient tradition to modern-day medicine. Evid Based Complement Alternat Med 2013; 2013: 915691.
3. Gertz HJ, Kiefer M . Review about Ginkgo biloba special extract EGb 761 (Ginkgo). Curr Pharm Des 2004; 10(3): 261-264.
4. Diamond BJ, Shiflett SC, Feiwel N, Matheis RJ, Noskin O, Richards JA, *et al* . Ginkgo biloba extract: mechanisms and clinical indications. Arch Phys Med Rehabil 2000; 81(5): 668-678.
5. Ding S, Dudley E, Plummer S, Tang J, Newton RP, Brenton AG. Quantitative determination of major active components in Ginkgo biloba dietary supplements by liquid chromatography mass spectrometry. Rapid Common Mass Spectrum 2006; 20(18): 2753-2760.
6. Mullaicharam AR. A review on evidence based practice of Ginkgo biloba in brain health. IJCPA 2014; 1(1): 24-30.
7. Roland PD, Nergård CS. Ginkgo biloba--effect, adverse events and drug interaction. Tidsskr Nor Laegeforen 2012; 132(8):956-959.
8. Maiuolo J, Oppedisano F, Gratteri S, Mus coli C, Mollace V. Regulation of uric acid metabolism and excretion. Int J Cardiol 2016; 213: 8-14.
9. Chaudhary K, Malhotra K, Sowers J, Aroor A. Uric acid key ingredient in the recipe for cardiorenal metabolic syndrome. Cardiorenal Med 2013; 3(3): 208–220.
10. Raina S, Agarwal VK, Kapoor D, Sharma KN, Yadav RS. Hypertension as determinant of hyperuricemia: a case control study from the sub-himalayan region in north india. J Asso Phys India 2018; 66 :14-18.
11. Ramirez MEG, Bargman JM. Treatment of asymptomatic hyperuricemia in chronic kidney disease: A new target in an old enemy – A review. J Adva Res 2017;8(5):551-554.
12. Chen W, Liu Y, Wei M, Shi L, Wu Y, Liu ZY *et al*. Studies on the effect of Ginkgo biloba L. leaves in acute gout with hyperuricemia model rats by using

UPLC-ESI-Q-TOF/MS metabolomic approach. RSC 2017; 7(68): 42964-42972.

13. Higuchi K, Umegaki E, Watanabe T, Yoda Y, Morita E, Murano M. Present status and strategy of NSAIDs induced small bowel injury. J Gastroenterol 2009; 44(9): 879-888.
14. Chan DC, Watts GF , Barrett PH, Burke VS. Waist circumference, waist-to-hip ratio and body mass index as predictors of adipose tissue compartments in men. Q J Med 2003; 96(6):441-447.
15. Fossati P, Berti G. Principle L, Use of 3,5-dichloro-2-hydroxybenzenesulfonic acid/ 4 aminophenazone chromogenic system in direct enzymatic assays of uric acid in serum and urine. Clin Chem1980; 26(2): 227-231.
16. Desideri G, Castaldo G, Lombardi A, Mussap M, Testa A, Pontremoli R *et al*. Is it the time to revise the normal range of serum uric acid levels?. Eur Rev Med Pharmacol Sci 2014; 18(9): 1295-1306.
17. Mahady GB. Ginkgo biloba for the prevention and treatment of cardiovascular disease: a review of the literature. J Cardiovasc Nurs 2002; 16(4): 21–32.
18. Elatrash AM, Abd El-Haleim SZ. Protective role of Ginkgo biloba on monosodium glutamate: induced liver and kidney toxicity in rats. RJPBCS 2015; 6(1): 1433-1441.
19. Owen PL, Johns T (1999). Xanthine oxidase inhibitory activity of northeastern north American plant remedies used for gout. J Ethnopharmacol; 64(2): 149-160.