# STUDY THE ANTIHYPERURICEMIC EFFECT OF SILYMARIN IN GOUTY ARTHERITIS RATS.

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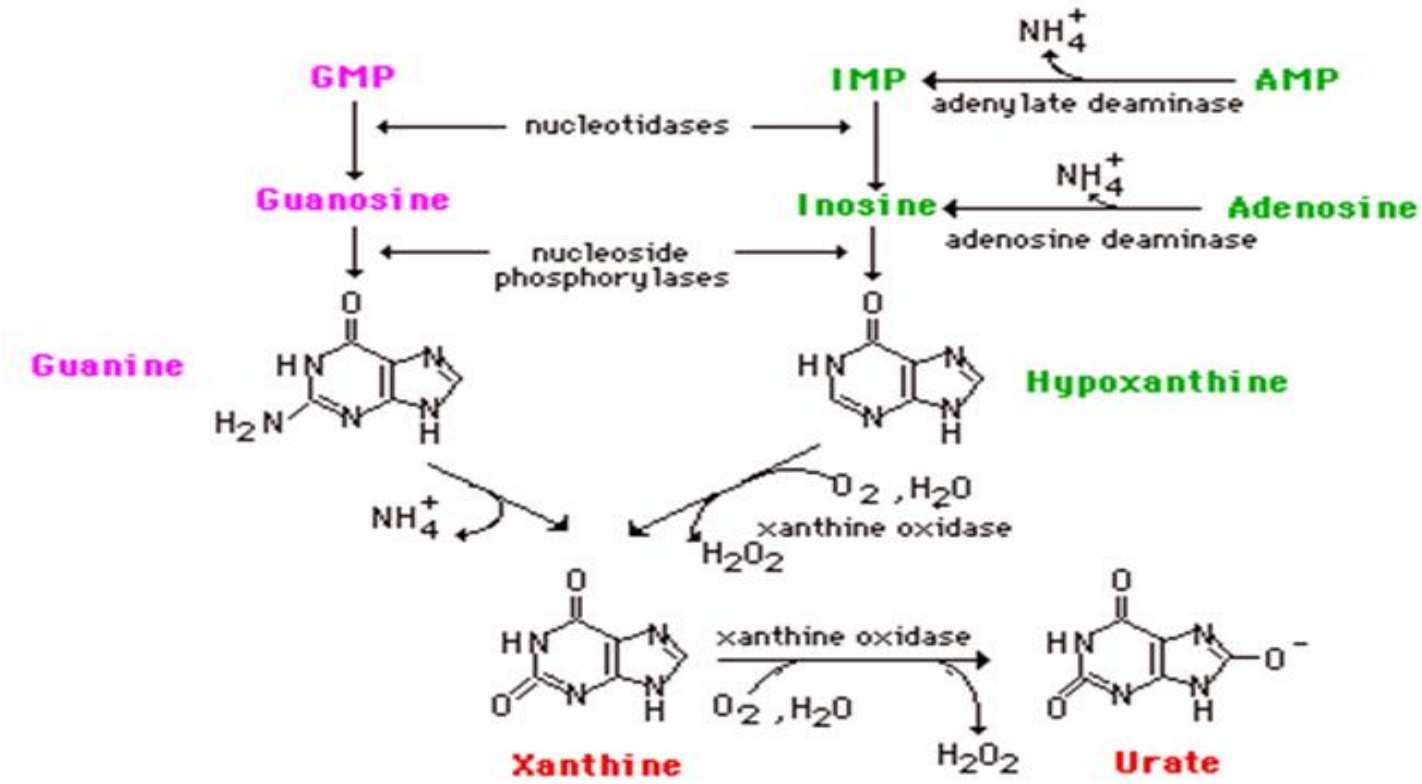
# OBJECTIVES:

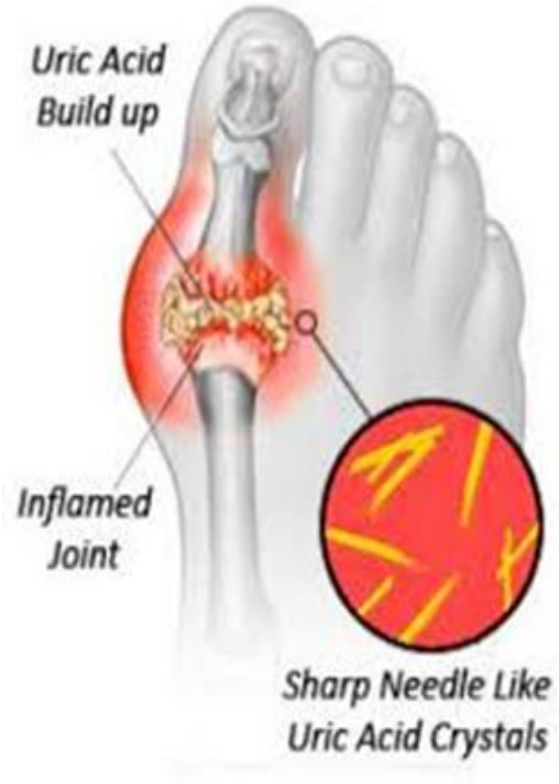
1. Hyperuricemia
2. Gout
3. Causes of hyperuricemia
4. Hyperuricemia associated conditions
5. Treatment of hyperuricemia
6. Silymarin

# HYPERURICEMIA AND GOUT :

- is an abnormally high level of uric acid in the blood. In the pH conditions of body fluid, uric acid exists largely as urate, the ion form. The amount of urate in the body depends on the balance between the amount of purines eaten in food, the amount of urate synthesised within the body (e.g., through cell turnover), and the amount of urate that is excreted in urine or through the gastrointestinal tract



High level of uric acid in the blood can cause “needle-shape” mono sodium urate crystals  that lead to GOUT ; which is painful condition result from deposition of MSU crystal in synovial fluid and form tophi



# CAUSES OF HYPERURICEMIA

## 1.Increased production of uric acid :

a. purine-rich diet is a common but minor cause of hyperuricemia
b. Tumor lysis syndrome produces extreme levels of uric acid.
c. The Lesch-Nyhan syndrome is also associated with extremely high levels of uric acid.

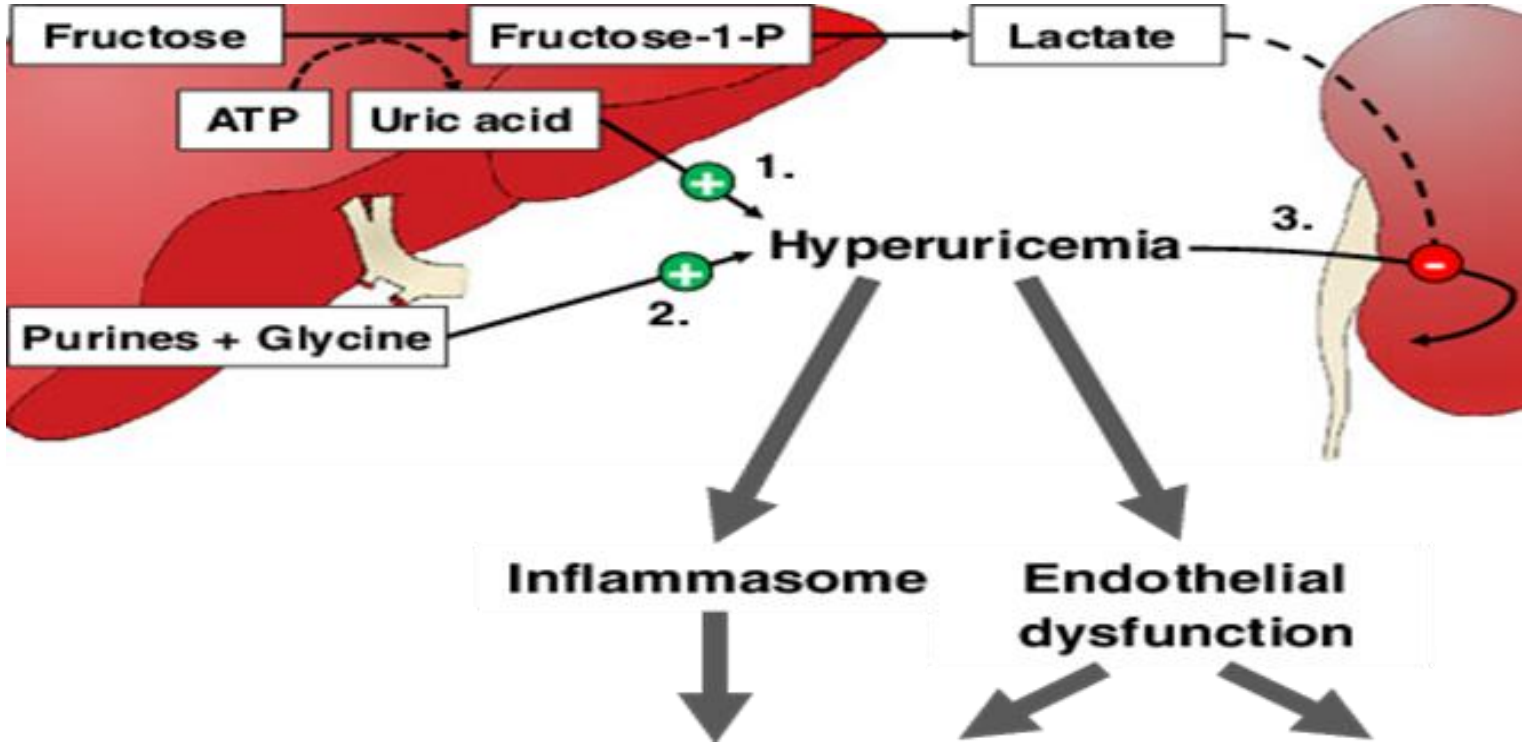
## 2.Decreased excretion of uric acid

a. Drugs ,include diuretics(thiazide,loope), salicylates, pyrazinamide, ethambutol, nicotinic acid, ciclosporin, and cytotoxic agents.
b. The gene SLC2A9 encodes a protein that helps to transport uric acid in the kidney.
c. A ketogenic diet impairs the ability of the kidney to excrete uric acid.
d. Elevated blood lead is significantly impaired kidney function.

## 3.Mixed type

Causes of hyperuricemia that are of mixed type have a dual action, both increasing production and decreasing excretion of uric acid.

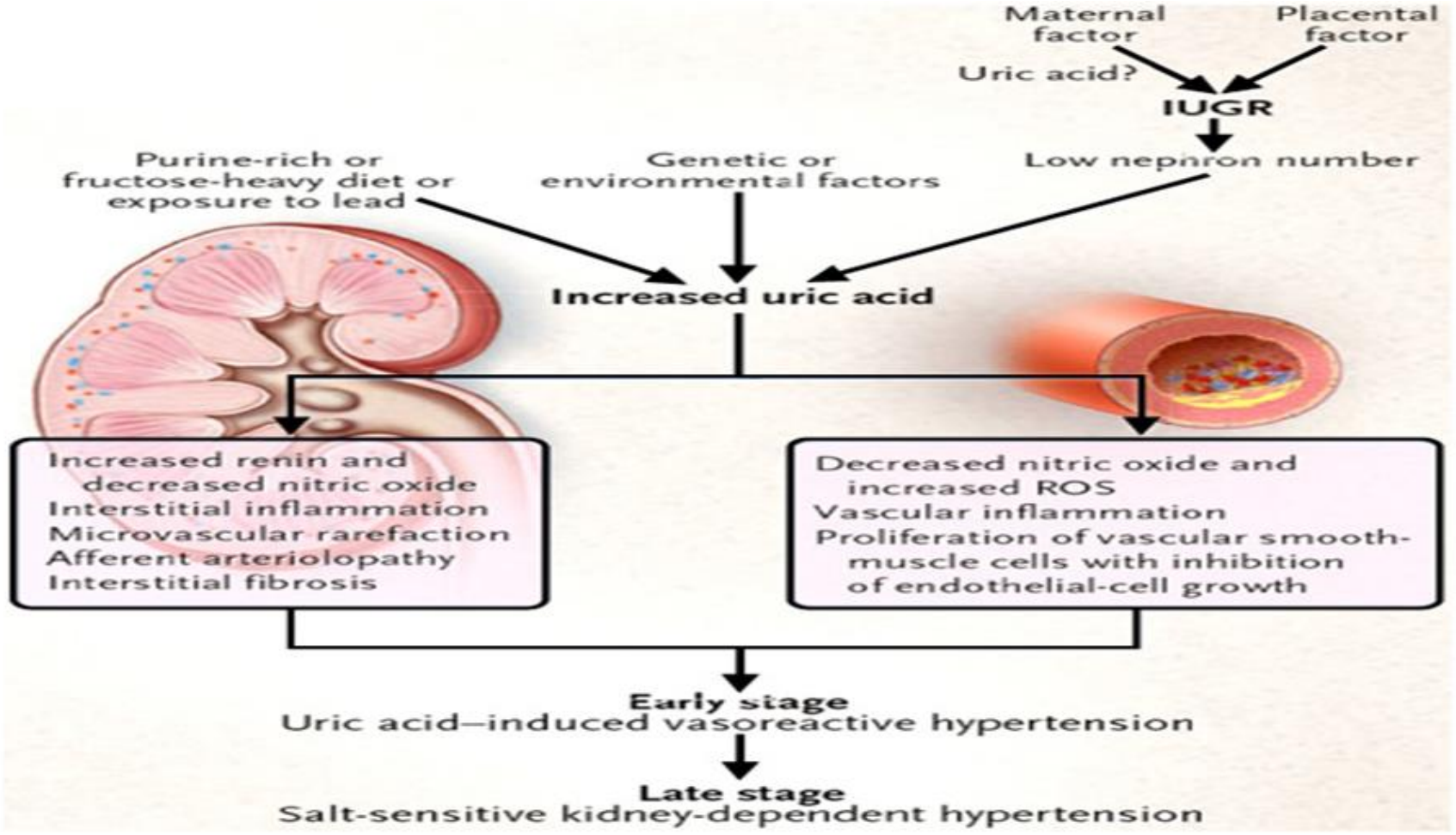
example: High intake of alcohol (ethanol), High dietary intake of fructose



# HYPERURICAEMIA-ASSOCIATED CONDITIONS:

## 1.Hypertension:

The mechanisms suggested are a renin-angiotensin-aldosterone-dependent arteriolopathy, inhibition of neuronal nitric oxide synthase, and glomerulosclerosis with albuminuria.

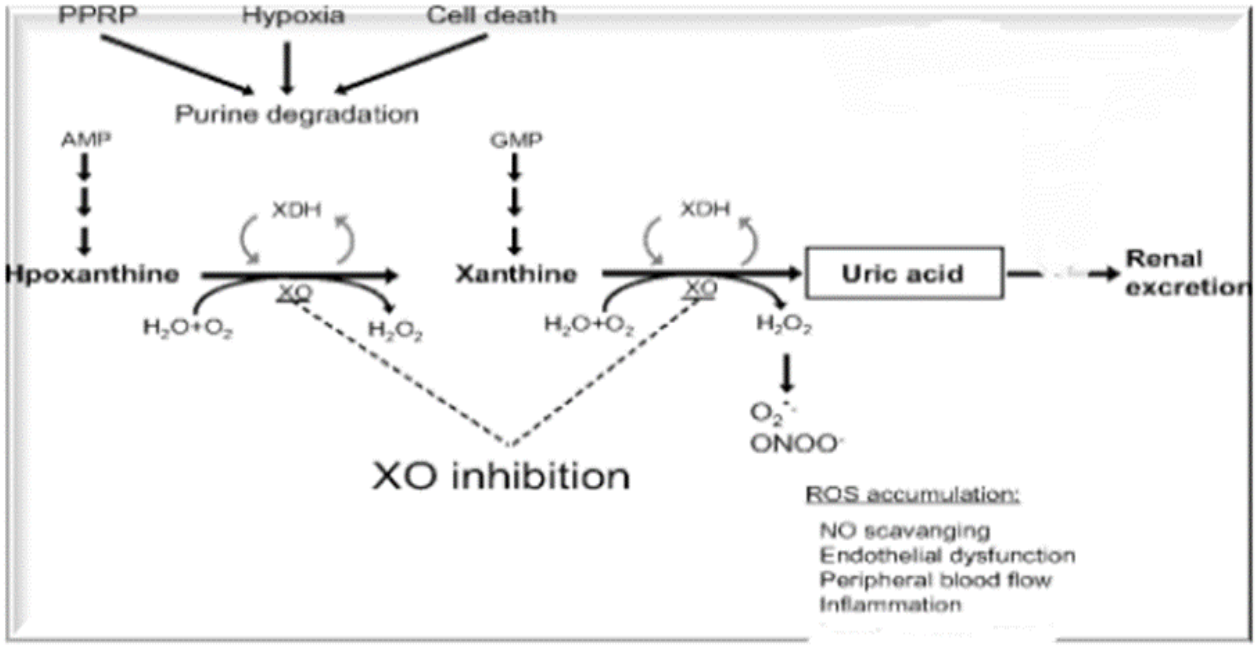


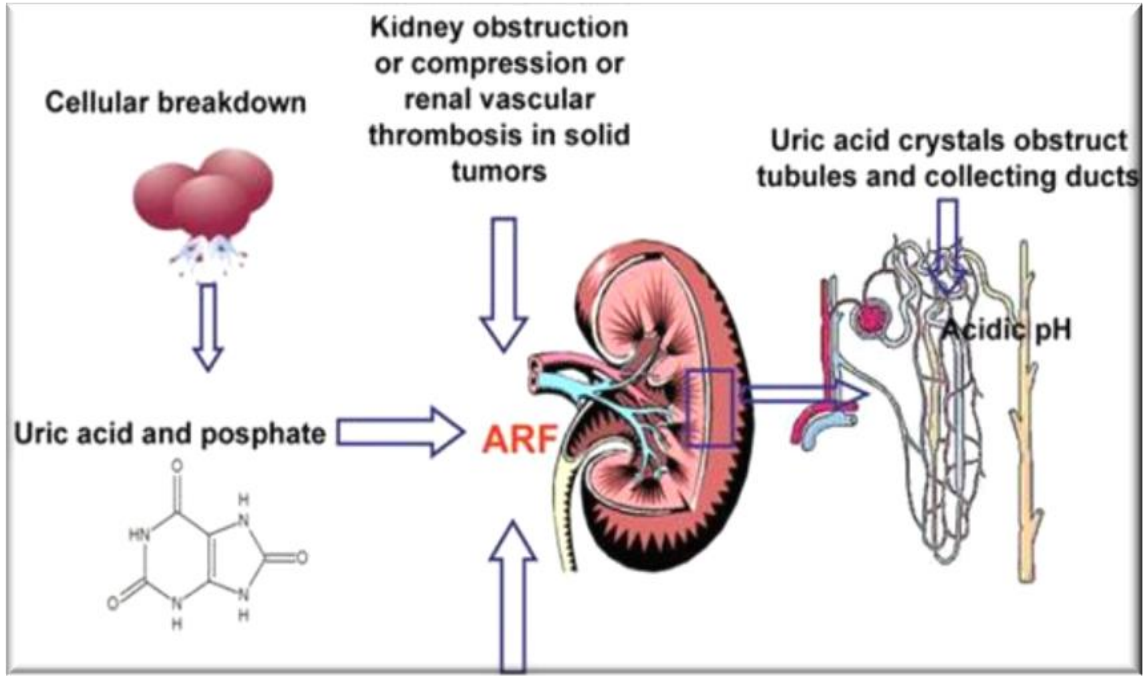
## .2.Chronic kidney disease (CKD)

Elevation of uric acid level lead to increase renin then vasoconstriction and decrease in GFR, and uric acid crystals obstruct tubules and collecting ducts.

## 3.Congestive heart failure (CHF)

increased XO activity in the failing myocardium, perhaps due to hypoxia and apoptosis, resulting in accumulation of uric acid precursors (hypoxanthine and xanathine) and XO-induced production of ROS, causing a vicious cycle of damage

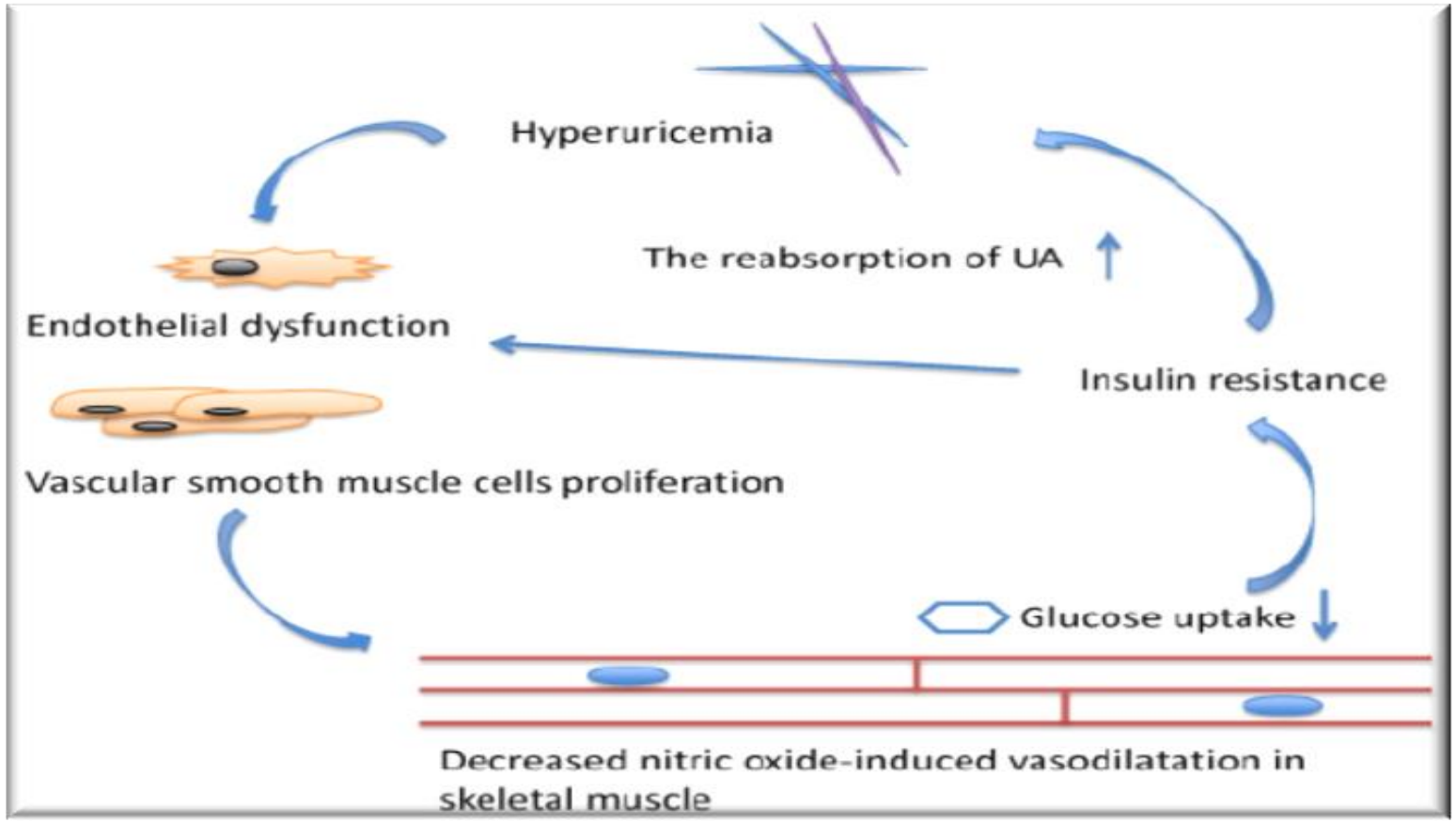


## 4.The metabolic syndrome, T2DM and obesity:

Two mechanisms are suggested: 1) hyperuricaemia-induced endothelial dysfunction, leading to reduced insulin stimulated nitric oxide-induced vasodilatation in skeletal muscle, and as a consequence reduced glucose uptake in skeletal muscle;

2) inflammatory and oxidative changes induced by intracellular urate levels in adipocytes.



# MANAGEMENT

-nonpharmacological management :

• Cherries are among the top foods that lower uric acid levels. They help prevent uric acid crystallization in the joints and they contain powerful compound called bioflavonoids

| Avoid | Limit | Encourage > |
|---|---|---|
| • Organ meats high in purine content (eg, sweetbreads, liver, kidney) B | Serving Sizes of:<br>• Beef, Lamb, Pork<br>• Seafood with high purine content (eg, sardines, shellfish) B | • Low-fat or non-fat dairy products B |
| • High fructose corn syrup-sweetened sodas, other beverages, or foods C | • Servings of naturally sweet fruit juices<br>• Table sugar, and sweetened beverages and desserts<br>• Table salt, including in sauces and gravies C | • Vegetables C |
| • Alcohol overuse (defined as more than 2 servings per day for a male and 1 serving per day for a female) in all gout patients B<br>• Any alcohol use in gout during periods of frequent gout attacks, or advanced gout under poor control C | • Alcohol (particularly beer, but also wine and spirits) in all gout patients B | |

# Pharmacological management: (Serum urate lowering agent )

## *1.xanthene oxidase inhibitors*

•Include Allopurinol and Febuxostat

•XOIs reduce endogenous production of uric acid by inhibition the conversation of hypoxanthine to xanthen and of xanthen to uric acid.

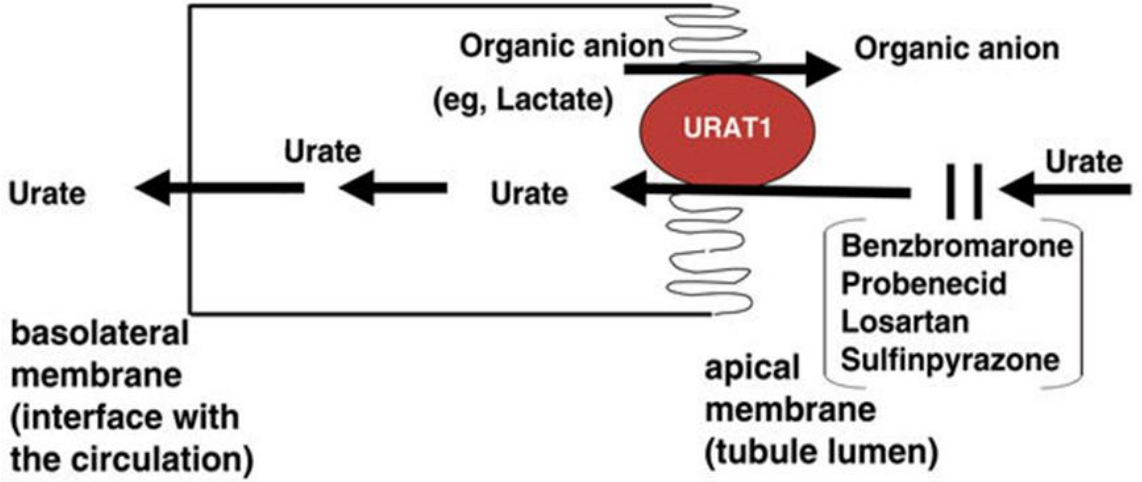
## Side effect:

•major side effects of *allopurinol* are skin rash, urticaria, leukopenia, GI problems, headache, and increased frequency of acute gouty attacks with the initiation of therapy.

•The most common side effect of febuxostat include liver function test abnormalities, diarrhea, headache, nausea, vomiting, abdominal pain, and dizziness.
*Safe in patients with renal insufficiency.

# 2.uricosuric drugs

- Act predominantly on urate anion exchange 1(URAT1), an organic anion transporter to prevent reuptake of uric acid at the proximal renal tubule and thus increase renal excretion of uric acid.




- The resulting higher concentration of uric acid in the collecting tubules can predispose to uric acid in the collecting tubules can predispose to uric acid stone formation, so the patient should be advised to drink plenty of fluids and remain well-hydrated
- Three uricosuric drugs are licensed and well established as ULT: benzbromarone (50-200mg daily), probenecid (250-500 mg twice daily), and sulfinpyrazone (200-800mg daily)
- Side effect: GIT disturbing, headache , dizziness, hepatic necrosis(rare), renal calculi and renal failure.
- The availability of benzbromarone became limited maily due to concerns over reports of hepatotoxicity.

- note: lipid lowering drugs of losartan and fenofibrate have mild uricosuric effect.

- Lesinurad (Zurampic), It received FDA approval 2015.
- is used in combination with a xanthine oxidase inhibitor, such as allopurinol, for treating hyperuricemia associated with gout. It is approved only for patients who have not achieved target uric acid levels with a xanthine oxidase inhibitor alone.
- Side effect :
- 1. serum creatinine was elevated in 4.3 to 7.8% of patients depending on the dose
- 2. Other common side effects were influenza , headache , and gastroesophageal reflux disease . Hypersensitivity reactions were rare.

## 3.uricase therapies:

Uricase an enzyme that converts uric acid to highly soluble allantoin

### Pegloticase :

use in treatment refractory gout.

Side effect :

Moderate to severe infusion reactions, so premedication with antihistamine and corticosteroids is need.

acute gout flares are seen in up to 80% of pegloticase-treated patients in the first few months of treatment, with flares tapering off later

### Rasburicase :

used in the prevention and treatment of chemotherapy-induced hyperuricemia

Side effect :rashes occurred in about 2% of patients, and bronchospasm, nausea and vomiting, and hemolysis less often.

# SILYMARIN

Silymarin is the active component of the milk thistle, which is a complex of other components, mainly silybin A, silybin B, isosilybin A, isosilybin B and also other flavonolignants.


**Applications**

1. Hepatoprotection
2. Prevention and treatment of Cancers
3. Neuronal effect
4. Protective effect on pancreas
5. Preventing effect against hemolysis
6. Protective effect against environmental toxin

## adverse effects

gentle gastrointestinal disturbance and mild allergic reactions, urticaria, nausea, headache, joint pain, itching, and mild laxative symptoms have been reported

# METHODOLOGY:

1. rats were separated into different experimental groups (n=6)
2. kept in the animals room under a regulated conditions at temperature 25±20 C and humidity 30±15% with 12-h dark/12-h light cycle for a week before being used for acclimatization.
3. Food, but not water, was withdrawn from the animals 2 h prior to drug administration
4. Silymarin was suspended in 0.5% sodium carboxymethylcellulose (CMC-Na).
5. Rats were orally administrated of Silymarin at 50 mg/kg once a day for seven consecutive days
6. Rats in the negative control group were orally administrated with 0.5% CMC-Na only, while those of the positive control group were given allopurinol at 10 mg/kg.
7. Hyperuricemia of rats was induced by potassium oxonate, was dissolved in 0.9% normal saline

8. One hour before administration of the silymarin, rats were intraperitoneally injected with the freshly prepared potassium oxonate solution at the dose of 250 mg/kg at first , third and seventh days of study period to increase their serum uric acid levels

9. Whole blood samples were collected from the tail vein of the rats 1 h after the final administration of tested compounds.

10. Determination of blood uric acid levels:

results:

| Negative control group | Post. Control with allopurinol | With silymarin |
|---|---|---|
| 4mg/dl | 1.6mg/dl | 3mg/dl |
| 3.8mg/dl | 1.1mg/dl | 2.4mg/dl |
| 3.7mg/dl | 1.7mg/dl | 3.2mg/dl |
| Average: 3.8 mg/dl | Avarage: 1.5 mg/dl | Avarage: 2.8 mg/dl |

Standered diveation of silymarin : 2.8 mg/dl (+/- 0.3)

Note : normal uric acid level: 0.5- 1.3 mg/dl

# DISCUSSION

- uric acid is a powerful scavenger of singlet oxygen, peroxyl radicals (RO·2) and hydroxyl radicals (·OH), to protects cells from oxidative damage
- In our study we used rats which preferred due to 90% gen similarity with human beings Also, many bodily systems of rats perform very much like human which makes it even more convenient to study the effect of silymarin.
- Rats injected with potassium oxonate work as uricase inhibitor (enzyme fond in all animals except human convert uric acid to allotoin) to elevate level of uric acid in rats and measure the effect of silymarin in ability to decrease its level.
- Potassium oxonate injected three times during a week, to keep level of hyperuricemia and measure antihypouricemic effect of silymarin.
- There are variable in the decreased level due to the drug given as oropharyngeal that may lead to loss during giving or variable in absorption.

- These result only in one week , may in long term administration decrease lower than that .
- Silymarin is a unique flavonoid complex—containing silybin, silydianin, and silychrisin.
- . Flavonoids have been shown to possess high activity for inhibition toward xanthine oxidase, and then t decrease uric acid levels in serum.
- Further step is need( we did not determined in this study) to measure the mechanism of silymarin in lowering uric acid by using uric acid kit (BioLab company France)

# CONCLUSION:

Hyperureicemia is abnormal elevation of uric acid in blood . many factors contribute to that abnormal level may be decrease excretion or increase production or mixied type. There are many drugs decrease uric acid level by working as xanthine inhibitor or have uricosuric effect. In our study we used silymarin to determine its effect as antihyperuricemic drug . after a week of giving silymarin to groups of rat (receiving potassium oxalate to elevate uric acid) the result found the blood concentration with silymarin was 2.86 +/-0.3 mg/dl .

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