

COLLEGE OF PHARMACY

UNIVERSITY OF BASRA

CLINICAL LAB.

SCIENCES DEP.

EFFECT OF ALPHA-LIPOIC ACID AS ANTIHYPERURICEMIA

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History of uric acid

The organic heterocyclic compound uric acid, discovered by the Swedish chemist Carl Wilhelm Scheele (1742–1786) and represented by the formula $H_2(C_5H_2N_4O_3)$, is the final product of purine catabolism. It derives from its precursor xanthine which is degraded by the enzyme xanthine oxidoreductase largely in the liver and the small intestine. Since, unlike most mammals, humans lack the very enzyme capable of degrading it into allantoin, they tend to have far higher uric acid levels, which throughout history have been linked to a constellation of clinical conditions, most notably gout.

Around 400 B.C. Hippocrates (466-377 B.C.), thought its cause was connected to the four humours (humors) which, if in balance in the body delivered health, and if out of balance delivered illness. The humours (humors) were blood, black bile, yellow bile and phlegm. The cause of gout he thought, was that an excess of one of these humours “dropped” or “gutta-d”, into a joint and hence the pain and inflammation therein. Tophi were accumulations of unbalanced humours (humors) in the affected body area such as an elbow joint.

Claudius Galen, (129 - 199-217 AD), physician to five Roman Emperors in the 2nd century AD, believed in an annual bleeding to re-balance the out-of-balance humours that had or would develop as a consequence of over eating and drinking, or of too much sexual activity (if you were a man – they didn't think women got gout until later in life, and generally that's correct). Antoni Van Leeuwenhoek was the first person in the history of gout to see gout's needle shaped crystals.

Carl Wilhelm Scheele a Swedish-German scientist who may have discovered oxygen before Joseph Priestley. In 1776 Scheele examined what he called urinary concretions (solid matter) and discovered a new acid, which he named lithic acid. It later became known as uric acid, most of which in the body is in the form of urate. In the same year his fellow countryman, Tobern Bergman analysed a bladder stone and found the same acid in it

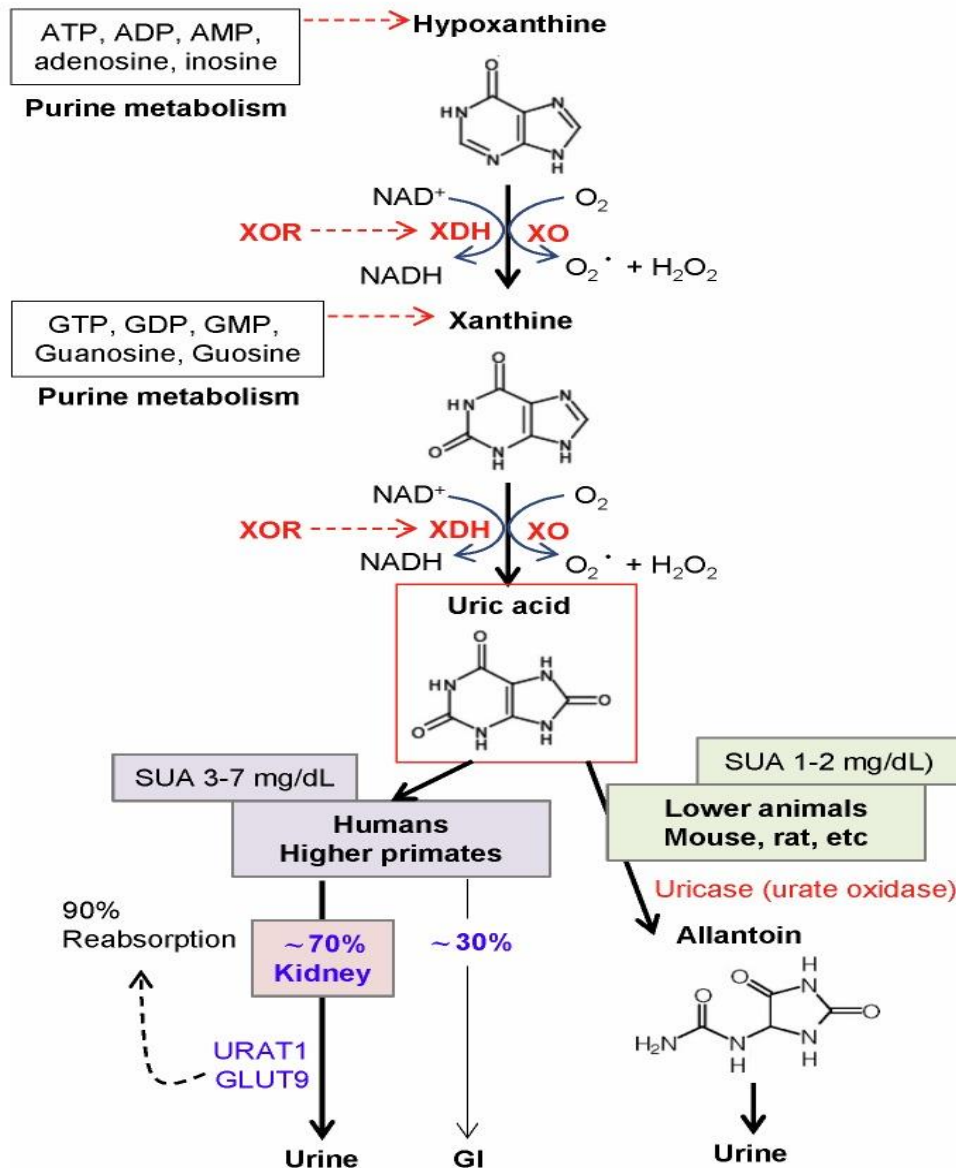
But the connection between uric acid and the chalky tophus crystals Leeuwenhoek had seen was not made. This would be the next major breakthrough in the history of gout, in fact a crucial breakthrough, and it came from Britain. In 1797, William Hyde Wollaston learnt that the same acid Scheele had found (lithic/uric acid) in urinary concretion

uric acid ;

Uric acid is a weak acid, with a ionization constant of acid (pKa) of 5.75-10.3. At the physiological pH of 7.40 of the extracellular compartment, 99% of uric acid is in the ionized form as urate (as monosodium urate in blood and as potassium, ammonium and calcium urate in urine). In the urinary tract, where pH can fall to 5.7, acid uric formation is favored...

synthises

Uric acid is the final product of purine nucleotide catabolism. In particular, purine nucleotides are derived from both endogenous (*de novo* molecule synthesis and nucleic acid breakdown) and exogenous sources (alimentary intake) *De novo synthesis of purines depends on* compound 5-phosphoribosyl-1-pyrophosphate, which is converted enzymatically to inosinic acid. In turn, it may additionally either be converted into bases for inclusion into nucleic acids or be broken down into xanthine to form uric acid



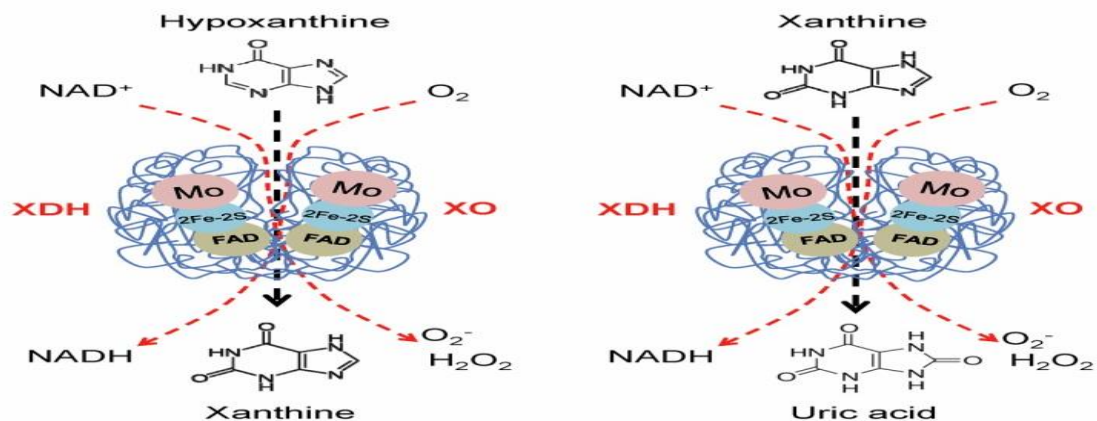
uric acid excretion:

The kidneys eliminate approximately two-thirds, while the gastrointestinal tract eliminates one-third of the uric acid load. Almost all uric acid is filtered from

glomeruli, while post-glomerular reabsorption and secretion regulate the amount of uric acid excretion. The proximal tubule is the site of uric acid reabsorption and secretion, and approximately 90% is reabsorbed into blood. The proximal tubule is the site of uric acid reabsorption and secretion, and approximately 90% is reabsorbed into blood. This is primarily accomplished at the proximal tubular level by transporters that exchange intracellular anions(such as lactate, ketone bodies, and xenobiotics through a counter-transport process)for uric acid. Almost all reabsorption of uric acid occurs at the S1 segment of the proximal tubule. In the S2 segment of the proximal tubule, uric acid is secreted to a greater extent than that which undergoes reabsorption. Post-secretory reabsorption occurs at a more distal site of the proximal tubule, and approximately 10% of the filtered uric acid appears in the urine.

Rule of XOR in formation of uric acid from xanthine

XOR is a critical, rate-limiting enzyme in purine metabolism. It catalyzes the last 2 steps of purine catabolism, the oxidation of hypoxanthine to xanthine and the oxidation of xanthine to uric acid, by utilizing either NAD^+ or O_2 . As a result of these reactions, 2 reactive oxygen species (ROS), superoxide anion (O_2^-) and hydrogen peroxide (H_2O_2), are produced. XOR is therefore a critical source of uric acid and ROS. XOR has 2 forms: xanthine dehydrogenase (XDH) and xanthine oxidase (XO). XDH prefers NAD^+ as the substrate and XO prefers O_2 . Most XOR in the liver exists in its XDH form, but it can be converted to XO form by reversible sulfhydryl oxidation or by irreversible proteolytic modification . XOR is also present in the intestines, mammary gland, cardiac and skeletal muscle, corneal epithelium, and endothelial cells of vascular vessels . During the oxidative hydroxylation of substrates, the Mo center receives 2-electron reduction from Mo (VI) to Mo (IV), and passes electrons via [2Fe-2S] clusters to the FAD cofactor .



Anti oxidant system of the body

An antioxidant is a molecule that inhibits the oxidation of other molecules. Oxidation is a chemical reaction that can produce free radicals, leading to chain reactions that may damage cells.. To balance the oxidative state, plants and animals maintain complex systems of overlapping antioxidants, such as glutathione and enzymes (e.g., catalase and superoxide dismutase) produced internally or the dietary antioxidants: vitamin A, vitamin C, and vitamin E.. Antioxidant dietary supplements do not improve health nor are they effective in preventing diseases. This includes supplements of beta-carotene, vitamin A, and vitamin E having no effect on mortality rate or cancer risk. Supplementation with selenium or vitamin E does not reduce the risk of cardiovascular disease...

The Oxidant-Antioxidant Paradox Mechanisms of Uric Acid

Uric acid exerts opposite effects on free radicals extracellularly or intracellularly. Circulating uric acid is believed to be a major aqueous antioxidant in humans, and it scavenges carbon centered radicals and peroxy radicals such as peroxynitrite (ONOO^-) in the hydrophilic environment and contributes to about 70% of all free radical scavenging activities in the plasma . For example, uric acid protects erythrocyte membrane against lipid peroxidation and lysis induced by t-butyl hydroperoxide . Uric acid can react with ONOO^- to form uric acid nitration/nitrosation derivatives that can release NO and induce vasorelaxation . Uric acid can also act as a chelator of iron in extracellular fluids .However, uric acid loses its radical scavenging activity and becomes a strong pro-oxidant under hydrophobic conditions. For example, uric acid can accelerate the copper-induced peroxidation of human LDL in the presence of pre-formed lipid hydroperoxides . In addition, when uric acid enters endothelial cells, vascular smooth muscle cells, monocytes, and other types of cells via specific organic anion transporters such as URAT1 , it induces intracellular and mitochondrial oxidative stress through multiple mechanisms such as the stimulation of NADPH oxidase ,and the production of pro-inflammatory cytokines such as monocyte chemoattractant protein-1 (MCP-1), high-sensitivity C reactive protein, interleukin-1, interleukin-6, interleukin-10, interleukin-18, endothelin-1, and tumor necrosis factor-alpha. Furthermore, uric acid blocks insulin- and vascular endothelial growth factor (VEGF)-mediated endothelial nitric oxide synthase (eNOS) activation and nitric oxide (NO) release ; induces cellular ER stress and eNOS dysfunction ; directly reacts with NO to form 6-aminouracil ; blocks the uptake of the substrate L-arginine ; and stimulates the degradation of L-arginine thereby reducing NO bioavailability). In liver cells, uric acid blocks AMP-activated protein kinase and stimulates gluconeogenesis . In adipocytes, uric acid induces oxidative stress and decreases adiponectin synthesis . Uric acid induces oxidative stress and inhibits growth of pancreatic β -cells . Uric acid stimulates vascular smooth muscle cell proliferation and induces inflammatory changes in the kidney . In renal proximal tubule cells, uric acid inhibits proliferation through the PKC signaling pathway . Overall, hyperuricemia contributes to the progression of cardiovascular disease and many other diseases through the oxidant property of uric acid.

Hyperuricemia

is defined as a plasma uric acid level greater than 6.8 mg/dL at physiological temperature (37°C) and neutral pH. Nevertheless, recent evidence has pointed out the importance of adapting this range to the population examined. For example, only serum uric acid levels lower than 6.0 mg/dL have to be considered normal in chronic hyperuricemic and gouty patients. As a matter of fact, this is the sole serum uric acid level truly preventing uric acid crystal deposition.

risk factors

- 1- unhealthy lifestyle that is mainly represented by a poor diet exceeding in purine nucleotides, protein, alcohol, and carbohydrates intake
- 2- various drugs must be considered potentially dangerous for purine nucleotides metabolism in patients having cardiovascular comorbidities and risk factors. Thiazides and loop diuretics both frequently cause hyperuricemia. Similarly, low-dose aspirin (primary and secondary cardiovascular prevention) decreases kidney excretion and thereby increases uric acid blood levels

Pathophysiology

Uric acid in the blood is saturated at 6.4-6.8 mg/dL at ambient conditions, with the upper limit of solubility placed at 7 mg/dL. Urate is freely filtered at the glomerulus, reabsorbed, secreted, and then again reabsorbed in the proximal tubule. The recent cloning of certain urate transporters will facilitate the understanding of specific mechanisms by which urate is handled in the kidney and small intestines. A urate/anion exchanger (URAT1) has been identified in the brush-border membrane of the kidneys and is inhibited by an angiotensin II receptor blocker, losartan. A human organic anion transporter (hOAT1) has been found to be inhibited by both uricosuric drugs and antiuricosuric drugs, while another urate transporter (UAT) has been found to facilitate urate efflux out of the cells. These transporters may account for the reabsorption, secretion, and reabsorption pattern of renal handling of urate

causes of hyperuricemia

1-Underexcretion accounts for most causes of hyperuricemia. Urate handling by the kidneys involves filtration at the glomerulus, reabsorption, secretion, and, finally, postsecretory reabsorption. Consequently, altered uric acid excretion can result from decreased glomerular filtration, decreased tubular secretion, or enhanced tubular reabsorption. While decreased urate filtration may not cause primary hyperuricemia, it can contribute to the hyperuricemia of renal insufficiency. Decreased tubular secretion of urate occurs in patients with acidosis (eg, diabetic ketoacidosis, ethanol or salicylate intoxication, starvation ketosis). The organic acids that accumulate in these conditions compete with urate for tubular secretion. Finally, enhanced reabsorption of uric acid distal to the site of secretion is the mechanism thought to be responsible for the hyperuricemia observed with diuretic therapy and diabetes insipidus.

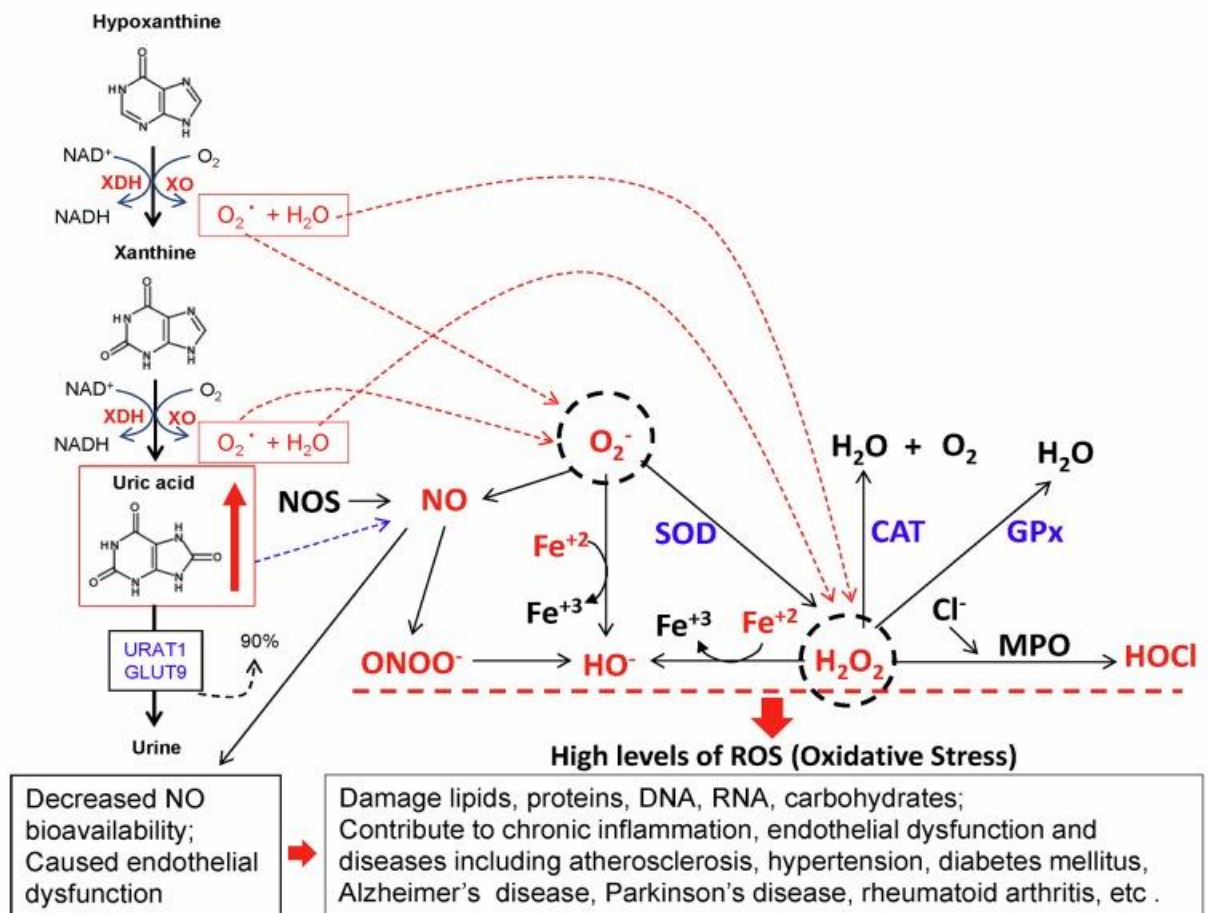
2-Overproduction accounts for only a minority of patients presenting with hyperuricemia. The causes for hyperuricemia in overproducers may be either exogenous (diet rich in purines) or endogenous (increased purine nucleotide

breakdown). A small percentage of overproducers have enzymatic defects that account for their hyperuricemia. These include a complete deficiency of hypoxanthine guanine phosphoribosyltransferase (HGPRT) as in Lesch-Nyhan syndrome, partial deficiency of HGPRT (Kelley-Seegmiller syndrome), and increased production of 5-phospho-alpha-d-ribosyl pyrophosphate (PRPP) activity. Accelerated purine degradation can result from rapid cell proliferation and turnover (blast crisis of leukemias) or from cell death (rhabdomyolysis, cytotoxic therapy). Glycogenoses types III, IV, and VII can result in hyperuricemia from excessive degradation of skeletal muscle ATP.

3-combined mechanisms (underexcretion and overproduction) can also cause hyperuricemia. The most common cause under this group is alcohol consumption, which results in accelerated hepatic breakdown of ATP and the generation of organic acids that compete with urate for tubular secretion. Enzymatic defects such as glycogenoses type I and aldolase-B deficiency are other causes of hyperuricemia that result from a combination of overproduction and underexcretion.

Molecular Mechanisms of Hyperuricemia-Related Diseases

Gout is a kind of arthritis caused by a buildup of uric acid crystals in the joints as a result of hyperuricemia. Furthermore, it has been hypothesized that hyperuricemia contributes to the progression of cardiovascular disease through oxidative stress, systemic inflammation, and endothelial dysfunction. As mentioned above, XOR produces O_2^- and H_2O_2 when it catalyzes the oxidation of hypoxanthine to xanthine to uric acid. O_2^- readily reacts with NO, reducing NO bioavailability, which is a main cause of endothelial dysfunction. In fact, the reaction between O_2^- and NO is 3 times faster than the O_2^- dismutation by superoxide dismutase (SOD). O_2^- and H_2O_2 not only directly cause oxidative damage to cells, but also can be converted to peroxynitrate ($ONOO^-$), hydroxyl anion (OH^-), and hypochlorous acid (HOCl), which are more toxic to the cells, by damaging proteins, lipids, carbohydrates, DNA, RNA, subcellular organelles, and cell systems. For example, $ONOO^-$ has a cytotoxic potential about 1000 times higher than that of H_2O_2 . Increased XOR activity and oxidative stress have been observed in cardiovascular disease in humans and experimental animals. Interestingly, high levels of XOR activity has been identified in human endothelial cells from the microvasculature of several tissues, and XOR is detected in the cytoplasm of endothelial cells and on the outer surface of the plasma membrane. Interestingly, circulating XOR can bind to the surface of endothelial cells by glycosaminoglycans (GAGs) and induce oxidative stress and endothelial dysfunction. Indeed, hyperuricemia-related endothelial dysfunction has been observed in both rats and humans, and inhibition of XOR has been shown to improve endothelial functions.



Epidemiology

United States

The prevalence rate of hyperuricemia in the general population is estimated at 20-25%, but only 4-6% in premenopausal women. {ref 38} The prevalence of gout is 5.9% in men and 2% in women.

International

The progressive increase in serum levels of uric acid levels may be linked to the rising prevalence of overweight and obesity, as well as the increase in consumption of sugar-sweetened beverages, foods rich in purines, and alcohol.

the prevalence increased among groups older than 65 years in both sexes. In those younger than 65 years, men had a prevalence 4 times higher than that in women, but in those older than 65 years, the gender gap narrowed to 1:3 (female-to-male ratio) with gout and/or hyperuricemia.

Race-, Sex-, and Age-related Demographics

A high prevalence of hyperuricemia exists in indigenous races of the Pacific, which appears to be associated with a low fractional excretion of uric acid. In the United States, African Americans develop hyperuricemia more commonly than whites.

Hyperuricemia, and particularly gouty arthritis, are far more common in men than in women. Only 5% of patients with gout are female, but uric acid levels increase in women after menopause. The normal serum uric acid level is lower in children than in adults. The upper limit of the reference range for children is 5 mg/dL (0.30 mmol/L). The upper limit of the reference range for men is 7 mg/dL (0.42 mmol/L) and for women is 6 mg/dL (0.36 mmol/L). The tendency to develop hyperuricemia increases with age

Hyperuricemia-Related Diseases

Gout: Condition characterized by abnormally elevated levels of uric acid in the blood, recurring attacks of joint inflammation ([arthritis](#)), deposits of hard lumps of uric acid in and around the joints, and decreased kidney function and [kidney stones](#). Uric acid is a breakdown product of purines, that are part of many foods we eat. The tendency to develop [gout](#) and elevated blood uric acid level (hyperuricemia)

Epidemiology

The annual incidence of gout in the US in people over 50 years of age is 1.6 per 1000 in men and 0.3 per 1000 in women.] The incidence increases with age. The annual incidence of gout in men increases from 1 per 1000 under 45 years of age, to 1.8 per 1000 at 55 to 64 years of age. Gout is more common in men and is rare in premenopausal women. The prevalence in the western world is about 1%, with a male to female ratio of 7:1 to 9:1. The prevalence varies geographically and racially. In New Zealanders with a European background, the prevalence is 3.6%. In the Maoris population, it is as high as 6.4%. The incidence of gout that is not associated with diuretic use has doubled over the past 20 years. This trend may be related to lifestyle changes and increased obesity.

Risk factor

StrongFactor, older age, male gender, menopausal status ,consumption of meat, seafood, alcohol use of diuretics, use of cyclosporine or tacrolimus, use of pyrazinamide, use of aspirin, genetic susceptibility, high cell turnover stat .. Weak Factor; adiposity and insulin resistance hypertension, renal insufficiency, diabetes mellitus hyperlipidemia

Pathophysiology

MSU crystals are in the extracellular space, while NOD-like receptors, which on activation form inflammasomes, reside in the cytoplasm. How do they interact? Macrophages take up the crystals, but then, the crystals are in the endosomal compartment, not in the cytosol. NOD-like receptors are cytosolic sensors that recognize either microbial PAMPs (pathogen-associated molecular patterns) or molecular features characteristic of distressed cells, so-called danger signals.

Distressed cells may bleed K⁺ or break down RNA and DNA, leading to formation of uric acid. One model that has been proposed works like this: Macrophages take up MSU crystals. Following fusion with acidic lysosomes, the decrease in pH causes the release of sodium from the crystals. Intracellular osmolarity increases, causing the cells to swell by influx of water. This has a short-time dilutive effect on intracellular K⁺ concentration, activating NOD-like receptor NALP3. Activated NALP3 units aggregate to form an inflammasome, which in turn activates caspase-1 to cleave proIL-1 β into IL-1 β

IL-1 β is just the leading ingredient of a macrophage-released cocktail that also includes TNF α , IL-6, CXCL8 (IL-8) and other inflammatory mediators. CXCL8 attracts neutrophils. These are activated and contribute to acute arthritis with production of reactive oxygen species, lysosomal enzymes, prostaglandins and leukotrienes

Signs and Symptoms

Signs and Symptoms Severe, throbbing, excruciating pain in a joint, particularly in the big toe (50% of cases), ankle or knee. The affected joint is inflamed – red, swollen, hot and very tender to the touch. Flu-like symptoms may appear, such as muscle aches and fever; hard nodules form on the joint surface; and physical movement is painful and difficult. Gout can also affect the ankles, knees, wrists, tendons and surrounding tissues. Complications Untreated gout may cause urate crystals nodules (tophi) to form under the skin.

Tophi can develop in several areas such as the fingers, hands, feet, elbows or Achilles tendons along the back of the ankle. Tophi themselves are not usually painful, but they can become swollen and tender during gout attacks. Another complication that may occur is the development of kidney stones due to urate crystals forming in the urinary tract.

Diagnosis:

- **Joint fluid test.** Your doctor may use a needle to draw fluid from your affected joint. Urate crystals may be visible when the fluid is examined under a microscope.
- **Blood test.** Your doctor may recommend a blood test to measure the levels of uric acid and creatinine in your blood. Blood test results can be misleading, though. Some people have high uric acid levels, but never experience gout. And some people have signs and symptoms of gout, but don't have unusual levels of uric acid in their blood.
- **X-ray imaging.** Joint X-rays can be helpful to rule out other causes of joint inflammation.

- **Ultrasound.** Musculoskeletal ultrasound can detect urate crystals in a joint or in a tophus. This technique is more widely used in Europe than in the United States.
- **Dual energy CT scan.** This type of imaging can detect the presence of urate crystals in a joint, even when it is not acutely inflamed. This test is not used routinely in clinical practice due to the expense and is not widely available

THE TREATMENT OF GOUT

- Options to alleviate acute attacks:

Colchicine has been used to treat gout since antiquity. It is a toxin from autumn crocus (*Colchicum autumnale*) that binds to tubulin and inhibits its polymerization. Microtubules are required for vesicle transport and for the mitotic spindle. Colchicine works well to alleviate the excruciating pain of an acute flare, but its use is a balancing act against its toxic side effects. Obviously, the oral drug reaches its highest concentrations in the gastrointestinal tract, **causing** nausea and other gastrointestinal symptoms. It is contraindicated at reduced creatinine clearance. Colchicine is most useful if patients have it at home, so that they are able to take it quickly in response to a flare

Glucocorticoids or corticotropin (ACTH) may be used in patients with reduced creatinine clearance. For their immunosuppressive effect, a potential infectious nature of the arthritis in question has to be excluded. Glucocorticoids may be injected directly in to the inflamed joint. Glucocorticoids inhibit expression and release of many cytokines, including IL-1 β .

Anti-IL-1 β -therapy: The importance of IL-1 β in the pathogenesis of gouty arthritis is underlined by the effectiveness of medications countering IL-1 β . However, compared to conventional therapy, these pharmaceuticals are extremely expensive and have the additional drawback of neutralizing a protein that is important for fighting infections. Apart, their effectiveness might encourage people to maintain unhealthy eating and drinking habits.

- **Anakinra** is a recombinant form of human IL-1 receptor antagonist, a protein that competitively blocks the IL-1 receptor. It was the first anti-IL-1 pharmaceutical, originally developed for rheumatoid arthritis, but gained little traction in that indication because anti-TNF α medication was more effective. In anecdotal cases, it was observed to be extremely effective in curbing flares of gout, which lead to renewed interest in anti-IL-1 β -therapy. Use of anakinra itself is limited by its very short half-life.

- **Canakinumab (Ilaris, Novartis)** is a monoclonal antibody against IL-1 β . It has been approved in the EU for patients with frequent flares of gouty arthritis who do not

respond to the drugs above or are unable to tolerate them. In a trial testing Canakinumab for cardiovascular benefits (CANTOS), participants developed more infections.

• **Rilonacept** (IL-1trap) is a fusion protein between IL-1 receptor and the Fc portion of IgG. It is used to treat rare cryopyrin-associated periodic syndromes (CAPS), but an FDA Advisory Panel did not recommend approval in gout because the benefits of the drug did not outweigh the risks.

NOTE: Options to bring down serum urate levels: As we have seen, levels of urate depend on production as well as elimination. Urate-lowering therapy may be initiated on either end, with pharmaceuticals available to either inhibit urate-producing xanthine oxidase or to enhance renal elimination. During the first weeks or months of urate-lowering therapy patients are at increased risk of a flare of disease, possibly by mobilization of urate from tissue deposits. Prophylaxis with colchicine or NSAIDS is attempted to prevent these flares.

Clinical XOR-Inhibitor Drugs

- Since XOR is a critical enzyme to produce uric acid and ROS, it becomes an effective target of drugs for the treatment of gout and hyperuricemia-related diseases, including cardiovascular disease, hypertension, kidney disease, and many other diseases
- The first XOR-inhibitor drug was allopurinol [4-hydroxypyrazolo (3,4-d) pyrimidine], which was discovered by American scientists, Nobel laureates Gertrude Elion and George Hitchings, in 1940s. It was approved by the US Food and Drug Administration (FDA) in 1966 for treating recurrent acute gouty arthritis, tophi, urate nephropathy, uric acid kidney stones, and chemotherapy-induced hyperuricemia .
- Allopurinol, a hypoxanthine analog, is hydrolyzed by XOR to produce oxypurinol, which binds tightly to the reduced molybdenum ion, Mo (IV), in the enzyme, and thus inhibits uric responsible for much of the pharmacological activity of allopurinol. Besides gout, allopurinol treatment significantly reduces the risk of myocardial infarction, reduces all-cause and cardiovascular mortality in high-risk patients, and improves endothelial functions . These encouraging clinical data have led to the increased use of allopurinol for these diseases . However, dueto acid synthesis .

Oxypurinol has long persistence in tissues and is its adverse effects, allopurinol is currently not indicated for broad use in asymptomatic hyperuricemia and its related cardiovascular disease, or in diseases other than gout. Asymptomatic hyperuricemia is a term traditionally applied to the condition in which the SUA level is elevated without symptoms or signs of uric acid crystal deposition disease, such as gout or uric acid renal disease. Asymptomatic hyperuricemia is a risk factor of cardiovascular disease and the other diseases mentioned above, Side effect

2–5% of treated patients experience adverse effects. Importantly, it is one of the most common drugs associated with life-threatening hypersensitivity reactions, including bone marrow depression, hepatotoxicity, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis, and drug rash with eosinophilia and systemic manifestations . These severe reactions with allopurinol occur in 0.1 to 0.4% patients, with a high mortality (27–32%) and a high morbidity, including renal failure and eye sequelae . The hypersensitivity reaction may occur even after months or years of medication.

The recently increased clinical use of allopurinol for cardiovascular and chronic kidney diseases showed a proportional increase in its induced-hypersensitivity reactions . Other adverse effects of allopurinol include peripheral neuritis, interstitial nephritis, renal toxicity due to impairment of pyrimidine metabolism, and congenital malformations when used during pregnancy .

Although the mechanism of allopurinol toxicity is not fully understood, it is hypothesized that the accumulation of its metabolite, oxypurinol, along with immunologic and genetic factors may modify the cellular proteins and trigger an autoimmune response against skin or liver cells

Febuxostat [2-(3-cyano-4-isobutoxy-phenyl)-4-methyl-1,3-thiazole-5 carboxylic acid] is a non-purine XOR-inhibitor drug approved by the European Medicines Agency in 2008 and US FDA in 2009 for use in patients intolerant to allopurinol . It was discovered by scientists at the Japanese pharmaceutical company Teijin in 1998. Febuxostat is structurally distinct from allopurinol and is able to inhibit both the oxidized Mo (VI) and reduced Mo (IV) forms of XOR, thus resulting in a more effective blockade of uric acid and ROS production . Clinically, febuxostat provides greater hypouricemic activity and less toxicity than allopurinol Side effect, initial clinical studies showed that febuxostat can also lead to cutaneous adverse effects in about 2% of patients . Cases of severe febuxostat hypersensitivity reactions such as SJS and anaphylactic shock are reported . These serious adverse effects with febuxostat are potentially associated with a history of skin reaction to allopurinol, particularly in patients with renal failure

febuxostat was associated with a higher incidence of hepatotoxicity in clinical patients . A case report also showed that febuxostat induced rhabdomyolysis . Thus, febuxostat is currently not recommended for the treatment of asymptomatic hyperuricemia .

Topiroxostat humans is not available due to its short duration of clinical use in Japan[4-[5-(4-Pyridinyl)-1H-1,2,4-triazol-3-yl]-2-pyridinecarbonitrile] is another XOR-inhibitor drug, approved in Japan in 2013 for the treatment of patients with hyperuricemia, including gout .Topiroxostat (formerly known as FYX-051) was discovered by Fujiyahujin Co. in Japan, and it is a non-purine, hybrid-type XOR-inhibitor, which not only forms a covalent linkage to molybdenum via oxygen in the hydroxylation reaction intermediate, but also interacts with amino acid residues of the solvent channel.Topiroxostat has high bioavailability and safety in animals. However, the information on its adverse effects in humans is not available due to its short duration of clinical use in Japan.

Uricosurics drugs

In the majority of patients, hyperuricemia is due to a reduced renal clearance of uric acid]. Hence it is reasonable to use drugs that increase urate renal excretion. Due to the low availability of specific drugs in many countries and safety concerns (especially with benzbromarone), uricosuric therapy is usually an option when the target SUA levels are not achieved or toxicity issues with XOI arise. In addition, in difficult-to-manage patients it is possible to combine a uricosuric drug with allopurinol or febuxostat to enhance SUA reduction [Due to the increase in urate renal excretion, caution with the use of uricosuric drugs in patients with a history of renal calculi is advisable and alkalinization of the urine is recommended to avoid renal calculi formation. Also, when the uricosuric is combined with a XOI the amount of uric acid excreted by kidneys is reduced by the effect of the latter, thus lessening the chances of developing renal stones

Benzbromarone is the most widely used uricosuric drug in Europe but it is unavailable in America. In 2003 it was withdrawn from the market after several cases of lethal liver toxicity were reported, but it remains available for restricted use in several European countries. It has afterwards been shown that benzbromarone has no more toxicity than allopurinol or colchicine and the withdrawal of benzbromarone from the market may have been unnecessary. In clinical trials no relevant differences have been found between benzbromarone and allopurinol in their ability to achieve SUA normalization, and no differences were found in withdrawals due to adverse events. Benzbromarone starting dose is 50 mg daily, to be increased in steps of 50 mg until the required maintenance dose is reached (maximum dose of benzbromarone is 200 mg daily). Benzbromarone can be used in patients with renal impairment at advanced stages of the disease and it is a valid option for transplanted patients using azathioprine or cyclosporine which limits the use of XOI due to drug interactions

Sulphinpyrazone is the only uricosuric drug generally available in the UK at present. It is usually prescribed at an initial dose of 100–200mg daily, increasing as required to 600mg per day. It should always be taken with food. Heartburn and stomach problems are the most frequent side effects. Allergic rashes can occur and on rare occasions sulphinpyrazone can have serious effects on the bone marrow and blood. • Sulphinpyrazone doesn't work well in people with reduced kidney function and it is best avoided by people who have had kidney stones. You should always drink lots of water when taking a uricosuric drug in order to avoid high concentrations of uric acid developing in your urine. High levels of uric acid in your urine can increase the likelihood of uric acid stones forming in your kidneys or bladder

Probenecid is recommended by ACR] guidelines and is available in America. In patients whose condition fails to respond to allopurinol the addition of probenecid has been shown to be effective. Probenecid is started at 500 mg daily, increasing to 1500–2000 mg daily to achieve target SUA

Common side effects include kidney stones, nausea, skin rash, stomach upset and headaches

Lesinurad is an oral drug that helps the body eliminate uric acid. It's used with a xanthine oxidase inhibitor (XOI), such as allopurinol or febuxostat, to enhance the effects for people whose gout is not controlled by optimally-dosed XOIs alone. Common side effects include headache, flu symptoms, increased blood creatinine,

gastroesophageal reflux disease (GERD), kidney-related side effects and kidney stones. Lesinurad may also increase the risk of cardiovascular events. Patients should stay well hydrated to avoid formation of kidney stones

Uricase

Unlike most mammals, upper primates and humans do not have a functional uricase. This enzyme degrades uric acid into allantoin, a more soluble molecule, easily eliminated through the kidney. With uricase treatment it is possible to achieve an immediate, significant reduction of SUA levels

Rasburicase is a recombinant uricase licensed for the treatment and prevention of tumour lysis syndrome which has been used in selected patients with severe gout . A monthly dose of rasburicase seems to be an effective option, but its short half life and the possible appearance of antibodies against the drug with repeated doses (in the authors' experience after fifth to sixth infusion) that reduces the drug effect and encourages hypersensitivity reactions should be noted. In addition, the sharp SUA reductions often result in severe gouty attacks in these patients, requiring intense prophylaxis schemes (such as prednisone 30 mg daily for 5 days).

Pegloticase is a pegylated uricase developed in an attempt to avoid immunogenicity issues and increase the half life of the drug. The effectiveness of this drug has been proved in severe cases of gout defined as 'three or more self-reported gout flares in the previous 18 months, 1 or more tophi, or gouty arthropathy'. Pegloticase is used intravenously 8 mg every 2 or 4 weeks. Preinfusion SUA level monitoring is recommended in order to reveal a loss of effectiveness, which should be suspected if SUA levels are higher than 6 mg/dl (0.36 mmol/liter). In this situation pegloticase should be discontinued as the SUA increase is associated with the development of pegloticase antibodies and an increased risk of infusion reactions. Other side effects can include gout flares, nausea, bruising, sore throat, constipation, chest pain

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Supplements **of Vitamin C** but not dietary Vitamin C alone have been shown to reduce the risk of developing gout in a study looking at men over a 20 year period. Those who had the highest vitamin C intake (both dietary and supplements) had the lowest risk of developing gout. Another study has demonstrated that Vitamin C 500mg daily lowers blood uric acid levels. In addition to ensuring that you have an adequate dietary intake of Vitamin C present evidence suggests that it could be helpful to supplement your diet with Vitamin C tablets (500–1500mg/day). If you do consider this, please make sure you discuss it with your GP as some prescription medicines can interact adversely with Vitamin C and higher doses can cause stomach upsets and diarrhoea. It is also important to understand that Vitamin C alone is not an adequate substitute for prescribed uric acid lowering drugs when these are indicated

ALPHA-LIPOIC ACID

Alpha-lipoic acid is a vitamin-like chemical called an antioxidant. Yeast, liver, kidney, spinach, broccoli, and potatoes are good sources of alpha-lipoic acid. It is also made in the laboratory for use as medicine.

Alpha-lipoic acid is most commonly taken by mouth for diabetes and nerve-related

symptoms of diabetes including burning, pain, and numbness in the legs and arms. It is also given as an injection into the vein (by IV) for these same uses. High doses of alpha-lipoic acid are approved in Germany for the treatment of these nerve-related symptoms.

Alpha-lipoic acid seems to help prevent certain kinds of cell damage in the body, and also restores vitamin levels such as vitamin E and [vitamin C](#). There is also evidence that alpha-lipoic acid can improve the function and conduction of neurons in diabetes. Alpha-lipoic acid is used in the body to break down carbohydrates and to make energy for the other organs in the body.

Alpha-lipoic acid seems to work as an antioxidant, which means that it might provide protection to the brain under conditions of damage or injury. The antioxidant effects might also be helpful in certain liver diseases.

Uses

Aging skin. Early research suggests that applying cream containing 5% alpha-lipoic acid might reduce fine lines and skin roughness caused by sun damage. Also, taking a specific product containing alpha-lipoic acid and other ingredients seems to improve elasticity and reduce wrinkles and roughness of aging skin.

Coronary artery bypass graft (CABG) surgery. Research suggests that taking a product containing alpha-lipoic acid, coenzyme Q10, magnesium, omega-3 fatty acids, and selenium up to 2 months before and 1 month after surgery seems to decrease complications following CABG surgery.

Diabetes. Taking alpha-lipoic acid by mouth or intravenously seems to improve blood sugar levels in people with type 2 diabetes. However, there is some inconsistent evidence that shows it does not affect blood sugar. Reasons for the inconsistencies may relate to the length of time that the patient has been diagnosed with diabetes, the use of antidiabetes drugs, or the purity of the alpha-lipoic acid treatment. Alpha-lipoic acid does not appear to improve blood sugar levels in people with type 1 diabetes.

Diabetic nerve pain. Taking 600-1800 mg of alpha-lipoic acid by mouth or by IV seems to improve symptoms such as burning, pain, and numbness in the legs and arms of people with diabetes. It may take 3 to 5 weeks of treatment for symptoms to improve. Lower doses of alpha-lipoic acid don't seem to work.

Weight loss. Research suggests that taking 1800 mg of alpha-lipoic acid daily for 20 weeks reduces body weight in people who are overweight. Lower doses of 1200 mg don't seem to work.

Possible Side Effects and Interactions of ALA

Alpha lipoic acid supplements haven't been studied in children or women who are pregnant or breastfeeding, so right now it's intended for use in adults only. Side effects of ALA in supplement form are generally rare but for some people can include: insomnia, fatigue, diarrhea, skin rash or low blood sugar levels (especially in people with diabetes or low blood sugar who are taking medications).

Some potential interactions, or circumstances where you want to speak to your doctor before taking extra alpha lipoic supplements, include: if you have a [thiamine deficiency](#) (vitamin B1), which is associated with [liver disease](#)/alcohol abuse, if you're taking any medications for diabetes for insulin control, since this can raise

the risk for [hypoglycemia](#) and low blood sugar, if you're recovering from chemotherapy treatment or taking cancer medications if you have a history of a thyroid disorder

ALPHA-LIPOIC ACID INTERACTIONS

Moderate Interaction Be cautious with this combination Medications for cancer (Chemotherapy) interacts with ALPHA-LIPOIC ACID, Alpha-lipoic acid is an antioxidant. There is some concern that antioxidants might decrease the effectiveness of some medications used for cancers. But it is too soon to know if this interaction occurs.

Minor Interaction Be watchful with this combination Medications for diabetes (Antidiabetes drugs) interacts with ALPHA-LIPOIC ACID. Alpha-lipoic acid might decrease blood sugar. Diabetes medications are also used to lower blood sugar. Taking alpha-lipoic acid along with diabetes medications might cause your blood sugar to go too low. But more evidence is needed to know if this interaction is a big concern. Monitor your blood sugar closely.

Some medications used for diabetes include glimepiride (Amaryl), glyburide (DiaBeta, Glynase PresTab, Micronase), insulin, pioglitazone (Actos), rosiglitazone (Avandia), chlorpropamide (Diabinese), glipizide (Glucotrol), tolbutamide (Orinase), and others.

Methods of our experimental

Animals:

Male Wistar rats (150-170 g) were supplied from animals' house unit of college of Pharmacy, University of Basrah. Both rats and mice were separated into different experimental groups (n=6), then the animals were accommodated in isolated plastic cages and kept in the animals room under a regulated conditions at temperature $25\pm 2^{\circ}\text{C}$ and humidity $30\pm 15\%$ with 12-h dark/12-h light cycle for a week before being used for acclimatization. They were fed standard chow and water ad libitum. All of procedures described in this study were authorized by Animal Ethics committee, University of Basrah, Iraq (no.2013/32).

Evaluation of anti-hyperuricemic effect

Drug administration:

Alpha-lipoic acid was suspended in 0.5% sodium carboxymethylcellulose (CMC-Na). Food, but not water, was withdrawn from the animals 2 h prior to drug administration. Rats were orally administered of Alpha-lipoic acid at 50 mg/kg once a day for seven consecutive days. 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.

Animal hyperuricemia model:

Hyperuricemia of rats was induced by potassium oxonate, an uricase inhibitor. In brief, potassium oxonate was dissolved in 0.9% normal saline . One hour before administration of the Alpha-lipoic acid, 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. Whole blood samples were collected from the tail vein of the rats 1 h after the final administration of tested compounds. Blood was allowed to clot for approximately 1 h at room temperature and then centrifuged at 3500 rpm for 5 min to obtain the serum, which was stored at -20 °C until used.

Determination of blood uric acid levels:

Serum uric acid levels were determined by the enzymatic kit method (BioLab., France).

Reference:

Thuy Duong Nguyen, Phuong Thien Thuong, Hyun Hwang, Thi Kim Huyen Hoang, Minh Khoi Nguyen., 17:191 (2017), *BMC Complementary and Alternative Medicine*.

Result of experiment :

Obtained the serum of uric acid from the three group of rats

Group of mice	Serum UA Conce.	Average value
+ve control group give allopurinol	1.6mg/dl	1.6 mg/dl
	1.7 mg / dl	
	1.6 mg / dl	

Group of mice	Serum UA Conce	Average value
_ve control group	4 mg /dl	3.83 mg /dl
	3.8 mg / dl	
	3.7 mg /dl	

Group of mice	Serum UA Conce	Average value
Alpha-Lipoic acid rats	1.2 mg/dl 2.1 mg /dl 1.9 mg /dl	1.73 ± 0.45

Discussion ;

Gout is a form of inflammatory arthritis that develops in some people who have high levels of uric acid in the blood. It occurs in about 4 percent of American adults, but is more likely to affect men than women , the first symptom of gout is excruciating pain and swelling in the big toe – often following a trauma, such as an illness or injury. Gout may also appear in another lower-body joint, such as the ankle or knee. Subsequent attacks may occur off and on in other joints, primarily those of the foot and knee, before becoming chronic .

Gout usually affects one joint at a time, but if left untreated it can affect many joints. Joint pain that used to resolve in a week to 10 days could become a milder, but constant pain. Eventually, untreated gout can cause other problems. Tophi – painless but disfiguring lumps of crystals formed from uric acid may develop under the skin around joints. The crystals can also form kidney stones.

Gout is associated with other serious health risks such as high blood pressure, diabetes, chronic kidney disease and cardiovascular disease ,

Low-Purine Foods“The specific reason why fructose is superior than glucose in increasing fat stores likely relates to the unique first steps in fructose metabolism. When fructose enters the hepatocyte, it is metabolized by a specific enzyme, fructokinase C. Unlike glucokinase, which has a negative feedback system to prevent excessive phosphorylation, the phosphorylation of fructose by fructokinase will proceed uninterrupted, and as a consequence intracellular phosphate depletion and ATP depletion frequently occur. The fall in intracellular phosphate results in the stimulation of AMP deaminase that helps accelerate the degradation of AMP to IMP and later to uric acid. In turn, the intracellular generation of uric acid results in oxidative stress.”

Antioxidants help fight oxidation, a normal chemical process that takes place in the body every day. It can be accelerated by stress, cigarette smoking, and alcohol. When there are disruptions in the natural oxidation process, highly unstable and potentially damaging molecules called free radicals are created. Oxygen triggers the formation of these destructive little chemicals, and, if left uncontrolled, they can cause damage to

cells in the body. It's much like the chemical reaction that creates rust on a bicycle or turns the surface of a cut apple brown. The human body is not without its own defenses against this damage. It creates many different types of molecules -- antioxidants -- to combat these free radicals and protect the cells from attack by oxygen. Antioxidants can safely interact with free radicals and stop the chain of damaging reactions before damage is done to cells. There are several enzyme systems in the body that scavenge free radicals, but we can also gain these helpful molecules from foods that we eat. Some vitamins are antioxidants, such as vitamins C and E. Some minerals are antioxidants, such as selenium and manganese, and there are plant compounds that act as antioxidants such as beta carotene and lycopene, terms you may have heard before or seen in ads for vitamin supplements,

Free radical formation occurs continuously in the cells as a consequence of both enzymatic and nonenzymatic reactions. Enzymatic reactions, which serve as source of free radicals, include those involved in the respiratory chain, in phagocytosis, in prostaglandin synthesis, and in the cytochrome P-450 system. Free radicals can also be formed in nonenzymatic reactions of oxygen with organic compounds as well as those initiated by ionizing reactions. Free radicals are not only generated by the body, they are present in foods you eat as well as in the air you breathe. Oxidative stress occurs when the production of free radicals goes beyond the protective defenses in the body. Oxidative stress and free radical damage to cells may initiate the early stages of cancer and heart disease. Free radicals are also suspect in the development of Alzheimer's disease, arthritis, cataracts, diabetes, kidney disease, and age-related blindness,

uric acid which have anti oxidant effect when the production of uric acid increase or excretion decrease lead to increase level of uric acid in body and since the production of uric acid is compained with oxygen species and hydrogen peroxide as by product of hypoxanthine conversion to xanthine Xanthine to UA so of alpha- lipoic acid work as antioxidant which act to previously knew for having antioxidant effect will inhibit XO enzyme

Lead to prevent uric acid synthesis; Alpha-lipoic acide was suspended in 0.5% sodium carboxymethylcellulose (CMC-Na). Food, but not water, was withdrawn from the animals 2 h prior to drug administration. Rats were orally administrated of Alpha-lipoic acide at 50 mg/kg once a day for seven consecutive days. The result of exper. Lowering of level of uric acid is (1.73 ± 0.45) so that LA antioxidant have good activity to decrease the level of serum uric acid of the rats when compered it is with result value of serim UA of rats that has been given allopurinol drug

Refreance;

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HISTORY OF URIC ACID IN THE URINE, WITH REFERENCE TO THE FORMATION OF URIC, ACID CONCRETIONS AND DEPOSITS BY

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