



## Review

# Uric acid in plants and microorganisms: Biological applications and genetics - A review



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## GRAPHICAL ABSTRACT



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## ABSTRACT

Uric acid increased accumulation and/or reduced excretion in human bodies is closely related to pathogenesis of gout and hyperuricemia. It is highly affected by the high intake of food rich in purine. Uric acid is present in both higher plants and microorganisms with species dependent concentration. Urate-degrading enzymes are found both in plants and microorganisms but the mechanisms by which plant degrade uric acid was found to be different among them. Higher plants produce various metabolites which could inhibit xanthine oxidase and xanthine oxidoreductase, so prohibit the oxidation of hypoxanthine to xanthine then to uric acid in the purine metabolism. However, microorganisms produce group of degrading enzymes uricase, allantoinase, allantoicase and urease, which catalyze the degradation of uric acid to the ammonia. In humans, researchers found that several mutations caused a pseudogenization (silencing) of the uricase gene in ancestral apes which exist as an insoluble crystalloid in peroxisomes. This is in contrast to microorganisms in which uricases are soluble and exist either in cytoplasm or peroxisomes. Moreover, many recombinant uricases with higher activity than the wild type uricases could be induced successfully in many microorganisms. The present review deals with the occurrence of uric acid in plants and other organisms specially microorganisms in addition to the mechanisms by which plant extracts, metabolites and enzymes could reduce uric acid in blood. The genetic and genes encoding for uric acid in plants and microorganisms are also presented.

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## Introduction

Uric acid is one of the most important nitrogen compounds in animal and plant bodies. It consists of 2,6,8 trihydroxypurine existing as a keto-enol tautomerism that under physiological conditions can easily be converted to the corresponding urate [1]. It derived from purine, two of which, adenine and guanine, are present in DNA and RNA. In Human, both uric acid and urate are accumulated in the form of calculi in the joints and/or connective tissues causing arthritis and rheumatic pain. They may also deposit in kidneys and/or ureters causing kidney disease or failure [2].

Uric acid is either produced when the body breaks purine occurred naturally [3] (Fig. 1) or supplied from certain foods. Consequently, some animal and plant foods with high purine contents should be avoided from diet especially in persons suffer from gout, as the overproduction of uric acid can induce hyperuricemia which is linked to gout [4].

The normal level of uric acid in the blood is between 3–7 mg/100 mL, which is required to human and animal bodies as antioxidant and prevents damage of blood vessels lining so protect them. Low purine diets including plants, often required to treat gout. The average daily meal for adult in United States contains about 600–1000 mg of purines. Recent research has shown that plant purines (fruits and vegetables) have risk of uric acid accumulation but lower than that of meat and fish [5].

## Production of uric acid by fungi and bacteria

Early, Jarmai [6] and Hutrya and Marek [7] reported that gout in birds had been caused by smut fungus *Ustilago maydis*, a common causal agent of moldy corn. Oosporin, a mycotoxin secreted by *U. maydis* induce gout in chickens and turkeys [8,9]. Furthermore, Constantini [10] reported that gout and hyperuricemia have been induced in animals by the fungal species *U. maydis*, *Chaetomium tri- alterale*, *Saccharomyces cerevisiae*, and *Candida utilis*. It is also induced by mycotoxins, aflatoxin, ochratoxin, Oosporin, and oxalic acid. Other fungal metabolites such as cyclosporine, ergotamine, and penicillin have been found to induce gout [10].

Gout is documented to be etiologically linked to beer, a *Saccharomyces* fermented beverage. Researchers found that beers contain significant quantities of ochratoxin and large amount of uric acid produced by the yeast *Saccharomyces* sp. [10] and accumulated in its vacuoles [11]. They also indicated that drinkers of beer and wine and people who often consume yeast foods such as bread and cheese are more susceptible to develop gout [10] (Table 1). Ochratoxin, a series of nephrotoxins produced by several species of the genera *Aspergillus* and *Penicillium* was found in beer and causes gout as early detected by many authors [10,12–14]. A synergistic interaction may occur between the alcohol from beer or yeast-fermented wine and ochratoxin. In fact, a study performed with 61 gouty men revealed that nearly all of them were beer drinkers [10].

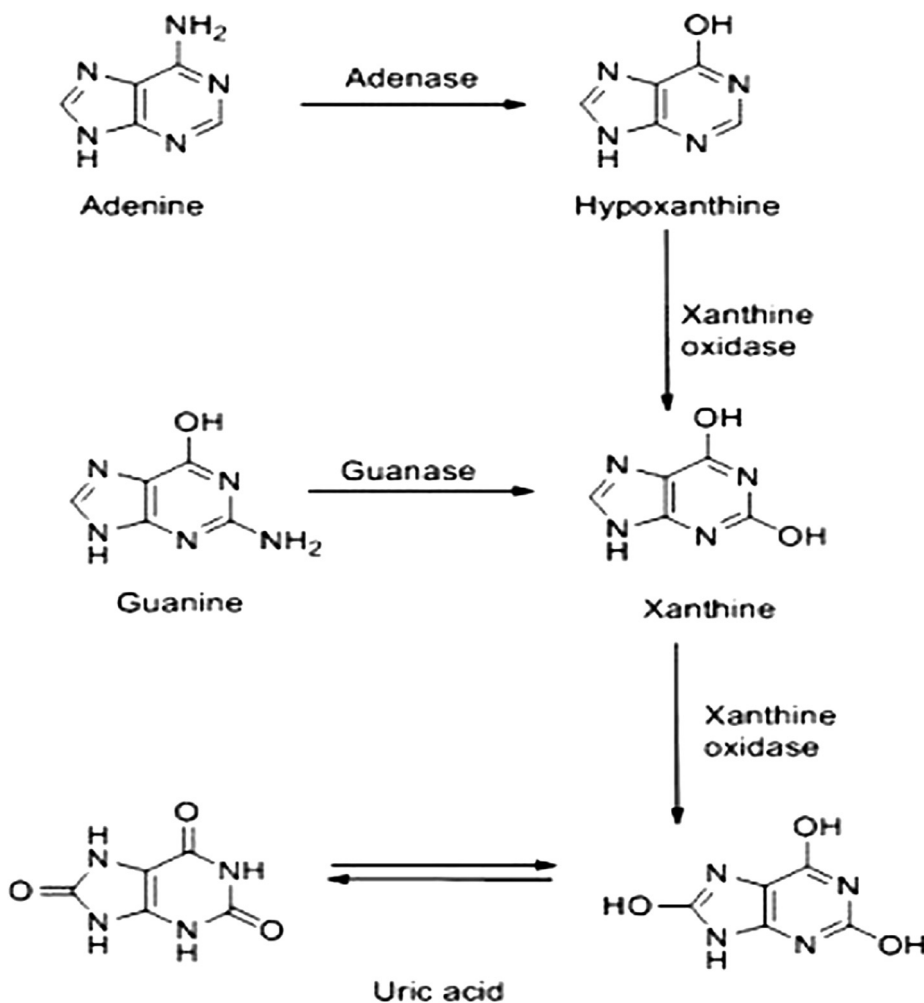


Fig. 1. Production of uric acid from purines. Adapted from Xiang et al. [3].

**Table 1**  
Uric acid content of various beers. Adapted from Constantini [10].

Brand of beer	Uric acid (mg/dL)
Miller beer	7.34
Olympia beer	7.05
Budweiser beer	8.09
Taiwan beer	9.35

Furthermore, long term feeding of rats with yeast autolysate has associated with rise in uric acid and anti-DNA antibodies. The elevated anti-DNA level was correlated with severe arthritis [15].

When single-cell protein, as in yeast, is used as a source of edible protein it increases uric acid in body when the individual lacks uricase [16]. Ergotamine, a fungal metabolite produced by *Claviceps purpurea*, and penicillin, an antibiotic produced by *Penicillium notatum*, has been shown to induce acute gout in human [17]. Aflatoxin, a common mycotoxin produced by *Aspergillus flavus* was also found to induce gout. When female Macaque monkey is fed with aflatoxin B1 contaminated food, numerous urate crystals surrounded by inflammatory cells were detected [18] and the kidneys lesions were similar to those found in human patients suffering from hyperuricemia and gout [19].

Oxalic acid, a metabolite produced by many fungal species, induced also, gout in human and chicken. It is one of the degradation products of uric acid. This explains why both oxalate and urate crystals are usually present in kidney stone of gouty patients [20].

Cyclosporine, a fungal metabolite produced by *Tolypocladium inflatum* and widely used as immunosuppressant, was found to be an inducer of gout in human. Many Organ Transplant Centers recorded that 24% of cyclosporine treated patients suffered from gout compared to patients treated with the immunosuppressant azathioprine where none of the patients suffered from gout [21–23].

Mushrooms and truffles contain moderate amounts of purine but are still included as a part of healthy diet because of additional benefits they provide. Moreover, Nogaim et al. [24] noticed an increase in uric acid level in blood serum of rats fed with mushroom powder after 15 days of daily diet due to much protein and phosphorus in mushroom. Continuous eating of this fungus can cause decrease in kidney function, leading to more serious high uric acid illness.

### Enzymatic degradation of uric acid by microorganisms

The enzyme responsible for purine metabolism is uricase (urate oxidase, oxidoreductase, EC 1.7.3.3). It activates the oxidation of uric acid to soluble allantoin. Most vertebrates possess uricase, except humans and higher apes, which became not functional by point mutation during evolution resulting in the formation of a redundant protein [25]. Uricase is localized inside microorganisms, especially *Bacillus pasteurii* [26], *Proteus mirabilis* [27], and *Escherichia coli* [28], while other microorganisms could produce them extracellularly by changing certain components of the culture media as in *Streptomyces albosriseolus* [29], *Microbacterium* [30], *Bacillus thermocatenuatus* [31], *Candida tropicalis* [32], and *Pseudomonas aeruginosa* [33].

### Microorganisms induced gout and hyperuricemia

Catabolism of purine to uric acid is conserved among microorganisms; however, the end product of uric acid breakdown varies among species, depending on the kind of active catabolic enzymes. The formed uric acid can either be excreted or degraded in the

peroxisomes by active catabolic enzymes [34], Fig. 2. Plants are capable to perform complete purine degradation. The end products, glycoxylate and ammonia, are recycled to synthesized organic molecules, which can be used in growth. Catabolic intermediates, urides, allantoin and allantoate, are likely to be involved in protecting plants against abiotic stress [35]. The first common intermediate of all purine bases is xanthine. It is oxidized to urate in the cytosol by xanthine dehydrogenase, whereas urate is imported into the peroxisome and oxidized by uricase to 5-hydroxyisourate, which in turn converted via 2-oxy-4-hydroxy-4-carboxy-5-ureidomidaoline to S-allantoin by the functional allantoin synthase [35–40]. In microorganisms, different end products of uric acid degradation are due to evolution of urate oxidase (uricase, allantoinase, and allantoicase). Moreover, most microorganisms possess all the required nitrogen catabolic enzymes to completely break down uric acid to ammonia [41–43]. In certain fungi and bacteria, allantoate is hydrolyzed by an allantolate amidinohydrolase (allantoicase) generating urea and s-ureidoglycolate [44–46], while in plants, it generate s-ureidoglycolate, ammonia and carbon dioxide from allantoate as final products [44,47,48]. In contrast to plant and microbes, animals degrade purine to intermediate purine compounds such as urates and allantoin, which are then excreted [34], Fig. 2.

El-Nagger and Emara [49] isolated from soil a number of uricolytic fungi belongs to *Fusarium*, *Spondilocladium*, *Stemphylium*, *Geotrichum*, *Mucor*, *Alternaria*, *Helminthosporium*, *Chaetomium*, *Penicillium*, *Curvularia* and *Aspergillus*.

Bacteria (*Pseudomonas*, *Enterobacter*, *Citrobacter* and *Lactococcus*) isolated from gut of apple snail *Pomacea canaliculata* possess high uricolytic activity. It symbiotically recycles the combined nitrogen and phosphorus in the snail [50]. Uric acid subjected to either non-enzymatic uricolysis to form antioxidant or enzymatic uricolysis to form allantoin and ammonia in the snail could afford amino acid, protein and purine [50–54], Fig. 3.

*Streptomyces exofolitus* isolated from soil by Magda et al. [55] were found to be high producer of uricase. They reported that this pure uricase can be used to diagnose and evaluate uric acid in urine and blood. Also, *Streptomyces albosriseolus* isolated by Ammar et al. [29] potentially produces uricase in media containing uric acid as carbon and nitrogen source.

The “Microbial Index of Gout” was declared as a novel, sensitive and non-invasive way for diagnosing gout via fecal microbiota. They proposed that the intestinal microbiota in gout patients is highly distinguished from that of healthy ones as *Bacterioides caccae* and *B. xylanisolvens* were enriched while *Faecalibacterium parusnitzii* and *Bifidobacterium pseudocatenuate* were depressed [56].

Ogawa [57] designed a new prophylaxis for treating hyperuricemia using probiotic effect of microorganisms as bacteria. The term probiotic refers to the living microorganisms that survive through the gastrointestinal tract and have beneficial effect on the host's health. He used pretreated rats with uricase inhibitor “Potassium oxonate” as a model for hyperuricemia. The serum uric acid level of the group treated with probiotics showed significant repression in rat serum specifically in the presence of *Lactobacillus fermentum* ONRIC b0185 and b0195 and *L. pentosus* ONRIC b0223. These bacterial strains could convert nucleosides to purine base because they have nucleosidases activities. Nucleosidases in turn convert guanine and adenosine to hypoxanthine then xanthine.

### Production of uric acid by plants

Hyperuricemia is highly affected by the high dietary intake of food rich in purine, such as meats, bean seeds, mushrooms and some types of sea foods [58]. Additionally, there is growing interest

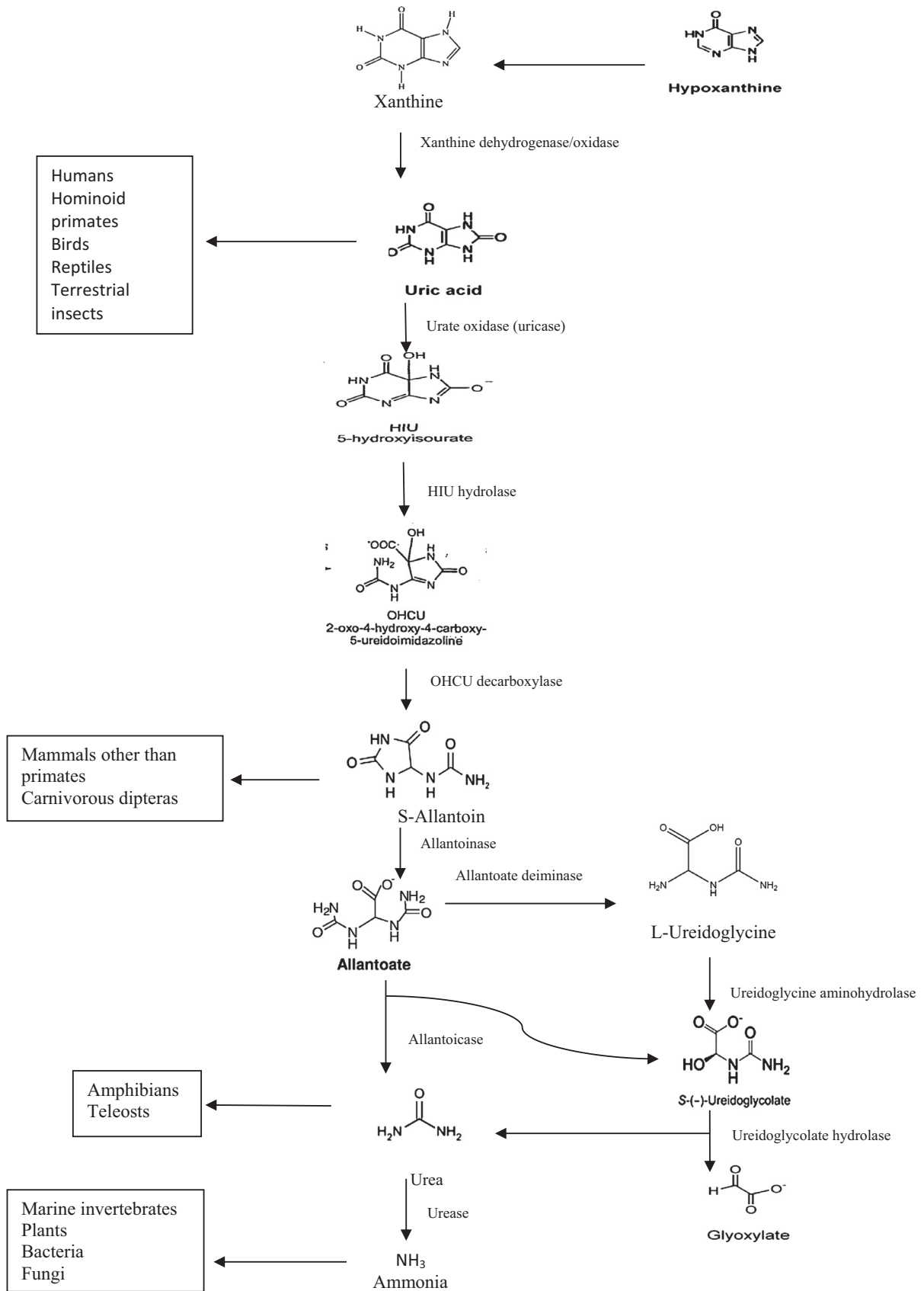


Fig. 2. Pathway of uric acid degradation to ammonia. Adapted from Lee et al. [34].

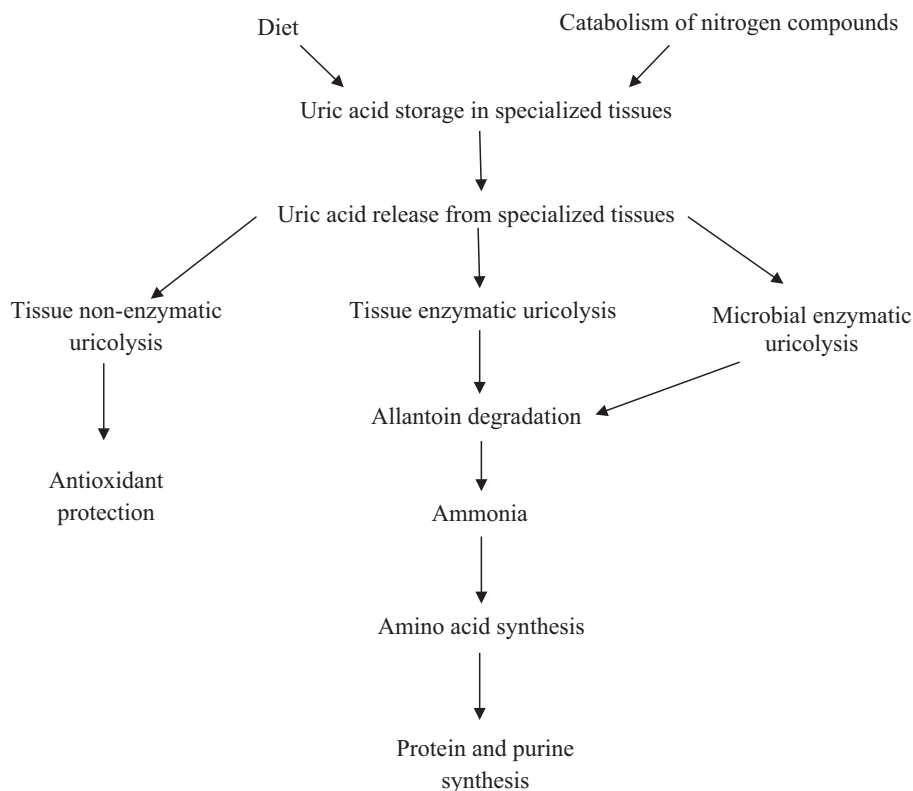


Fig. 3. Catabolic pathway of uric acid in tissues. Adapted from Koch et al. [50]; Vega et al. [51], and Giraud-Billoud et al. [52–54].

in fruits, vegetables and herbs high in phytochemical compounds that have been implicated as alternative or additive drugs to gout.

Purines are naturally occurred in all plant foods. It was found that purine at 10–15 mg/100 g food is present in all plant foods. However, some plant foods can contain 100–500 mg uric acid/100 g food [59]. However, some others contain above this range. Plants which have high amounts of purines include spinach, peas, lentils, cauliflowers and beans. Any food containing yeast extract should be avoided [60]. Several plants contain moderate concentrations of purine ranging from 50–100 mg/100 g of food, as avocado, bananas and asparagus [61], (Table 2), in which one should not consume them on weekly basis in portions larger than one small cup (in fresh state) or half cup (if in cooked state). Some foods, on the other hand, are helped in decreasing uric acid level such as pineapple, lemons, fibrous foods, olive oil, parsley, red cabbage, corn and rice [60].

Vegetables containing higher levels of magnesium and lower level of calcium reduce the amounts of uric acid in the blood and decrease the chance of developing gout. These vegetables include corn, potatoes and avocados. Celery seeds are popular alternative to drugs in reducing uric acid in blood. Furthermore, fruits and vegetables contain vitamin C may help in the reduction of uric acid level in blood. Cherries especially black cherry juices being used in great quantities to help relief the symptoms of gout and reduce uric acid level [62].

### Inhibition of uric acid synthesis by some plant metabolites

Xanthine oxidoreductase (XOR) has two forms; xanthine oxidase (XO) and xanthine dehydrogenase (XDH), both of them catalyze the oxidation of hypoxanthine to xanthines, then to uric acid in the purine metabolism [4]. Overactivity of both enzymes cause the accumulation of uric acid in the body and form a

pathogenesis condition called gout [63]. Additionally, xanthine oxidase (XO) serves as a valuable biological source of oxygen free radicals that participate in various damages of living tissues leading to many pathological states [58,64].

Some herbal plant extracts possess antioxidant activity to abolish the oxidative and inflammatory response produced by xanthine oxidase. Xanthine oxidase [XO EC.1.2.3.2] is a key enzyme that plays a role in hyperuricemia catalyzing the oxidation of hypoxanthine to xanthine then to uric acid. The enzyme is situated at the end of the catabolic sequence of purine metabolism [65]. Therefore, several researches are focused on exploring potent XO inhibitors from wide variety of traditional herbal plants [66,67].

Allopurinol is the efficient clinically used XO inhibitor in the treatment of gout [68]. However, this drug causes numerous side effects such as nephropathy and allergic responses [69]. Thus the search for natural XO inhibitors from plants with higher therapeutic activity and fewer side effects are needed to treat gout and other diseases associated with XO activity. Some medicinal plants represent a potential source of XO inhibitors [67,70]. Plant flavonoids, anthocyanins and phenolics are known to have antioxidant and anti-inflammatory properties that reduce uric acid in blood [71–73].

The presence of uricases in plant was established in glyoxysomes of different seed tissues (endosperm, perisperm, scutella and cotyledons) from various plants [74] as well as in peroxisomes from maize root tips [75], soybean nodules [76], in roots but not in leaves of corn and tobacco [74], in pea and soybean leaf extracts [77] and from leaves of chickpea, broad bean and wheat [78].

Many herbal plant species were explored to be antigout and reduce uric acid in blood such as *Lagerstroemia speciosa* [4], *Apium graveolens*, *Ficus carica*, *Curcuma domestica*, *Cinnamomum zeylanicum* and *Rosmarinus officinalis* [79], *Erythrina strica* [80], *Rhus coriaria* [81], *Juniperus phoenicea* [82], *Momordica charantia*, *Apium graveolens*, *Petroselinum crispum*, *Linum usitatissimum*, *Cucurbita pepo*,

**Table 2**  
Occurrence of uric acid in plant foods. Adapted from Halevi [61].

Plant foods	Total uric acid mg/100 g food (average)	Plant foods	Total uric acid mg/100 g food (average)
<i>Highest in uric acid (400 mg/100 g and higher)</i>			
Mushroom, flat, edible Boletus, dried	488	Yeast, Baker's	680
<i>Moderately High in uric acid (100–400 mg/100 g)</i>			
Bean, seed, white, dry	128	Bean, Soya, seed, dry	190
Black gram (mungo bean), seed, dry	222	Grape, dried, raisin, sultana	107
Lentil, seed, dry	127	Linseed	105
Peas, dry, chick (garbanzo), seed	109	Poppy seed, seed, dry	170
Sunflower seed, dry	143		
<i>Lower in uric acid (100 mg/100 g and lower)</i>			
Almond, sweet	37	Apple	14
Apricot	73	Artichoke	78
Asparagus	23	Aubergine	21
Avocado	19	Bamboo shoots	29
Banana	57	Barley without husk, whole grain	96
Bean sprouts, Soya	80	Bread, wheat (flour) or White bread	14
Broccoli	81	Brussel sprouts	69
Cabbage, red	32	Cabbage, savoy	37
Cabbage, white	22	Carrot	17
Cauliflower	51	Celeriac	30
Cherry, Morello	17	Cherry, sweet	7.1
Chicory	12	Chinese leaves	21
Chives	67	Cocoa powder, oil partially removed	71
Corn, sweet	52	Cress	28
Cucumber	7.3	Currant, red	17
Date, dried	35	Elderberry, black	33
Endive	17	Fennel leaves	14
Fig. (dried)	64	Gooseberry	16
Grape	27	Grass, Viper's (black salsify)	71
Kale	48	Kiwi fruit (Chinise gooseberry, strawberry peach)	19
Kohlrabi	25	Leek	74
Lettuce	13	Melon, Cantelope	33
Millet, shucked corn	62	Morel	30
Nuts, Brail	23	Nuts, hazelnut (cobnut)	37
Nuts, peanut	79	Oats, without husk, whole grain	94
<i>Lower in uric acid (100 mg/100 g and lower)</i>			
Olive, green, marinated	29	Onion	13
Orange	19	Parsley, leaf	57
Pea, pod and seed, green	84	Pea, seed, dry	95
Peach	21	Peppers, green	12
Pineapple	55	Plum	19
Plum, dried	24	Potato	64
Pumpkin	18	Quince	44
Radish	30	Raspberry	18
Rhubarb	12	Rye, Whole grain	51
Sesame (gingelly) seed, oriental, dry	62	Spinach	57
Squash, summer	24	Strawberry	21
Tomato	11	Wheat, whole grain	51

*Zingiber officinale*, *Curcuma longa*, *Cinnamomum* sp., *Rosmarinus* sp. [56,83], *Origanum majorana* [84], *Prunus cerasus* [85], *Phyllanthus niruri* [86], *Glycine max* and *Arabidopsis thaliana* [87], *Vinca* sp. [10,88] and *Colchicum* sp. [10,89–91]. The mechanisms by which these plants reduce uric acid in blood were summarized in Table 3.

### Genetics and uricase encoding genes

Schult et al. [92] discovered 14 functional genes encoding enzymes or proteins of the purine catabolic pathway. Five genes (*pucA*, *pucB*, *pucC*, *pucD*, and *pucE*) must be expressed for the function of xanthine dehydrogenase, while only 2 genes (*pucl* and *pucM*) were encoded for uricase, and *pucJ* and *pucK* genes encoded the uric acid transport system. The *pucH* and *pucl* genes encoded allantoinase and allantoin permease, respectively. On the other hand, allantoinamide amidohydrolase is encoded by *pucF* gene. The

*pucR*-mutant *Bacillus subtilis* expressed low activity of all tested genes, indicating that PucR is the main regulator of *puc* genes expression. All 14 genes except *pucl* are located at 284–285° in the gene cluster on the chromosome and are implicated in six transcription units. Allantoic acid, allantoin, and uric acid were effector compounds that regulate PucR for the expression of *puc* genes.

Uric acid utilization activates the production of the virulence factors (capsule and urease) in the pathogen *Cryptococcus neoformans* (the cause of fatal meningitis in the immune-compromised patients), that potentially regulate the immune response in the host during infection. The identified catabolic genes of uric acid in *C. neoformans* were *URO1* (urate oxidase), *URO2* (HIU hydrolase), *URO3* (OHCU decarboxylase), *DAL1* (allantoinase), *DAL2,3,3* (allantoicase-ureidoglycolate hydrolase fusion protein), and *URE1* (urease) [34].

In Humans, multiple independent evolutionary events cause the pseudogenization (silencing) of the uricase gene in ancestral apes [93]. Uricase exists as insoluble crystalloid that involves the core



**Table 3**

The mechanisms by which some plant active metabolites reduce uric acid in blood.

Plant species	Family	Used part	Active metabolite	Mechanism of action	References
<i>Lagerstroemia speciosa</i> (L.) Pers.	Lythraceae	Leaves	Valoneic acid dilactone (VAD) Ellagic acid (EA)	Inhibit xanthine oxidase (XO)  <div style="text-align: center;">           Hypoxanthine            ↓ Xanthine oxidase            Xanthine            ↓            Uric acid            ↓            Hyperuricemia         </div>	[4]
<i>Apium graveolens</i> (Celery)	Umbelliferae	Fresh leaves and seeds	Oleic and Linoleic acid in Celery All rich in phenolics	Antigout, antimicrobial, Anti-inflammatory and antioxidant effects	[79]
<i>Ficus carica</i> (Fig)	Moraceae	Dry Fig. fruits	Unsaturated fatty acids, long chain fatty acids, phytosterols and Malondialdehyde		
<i>Curcuma domestica</i> L. (Turmeric)	Zingiberaceae	Rhizomes			
<i>Cinnamomum zeylanicum</i> (Cinnamon)	Lauraceae	Bark			
<i>Rosmarinus officinalis</i> (Rosemary)	Labiatae	Leaves	Flavonoids, saponins, tannins, phenolics and triterpenoids	Inhibit xanthine oxidase (XO) and xanthine dehydrogenase (XDH) activities	[80]
<i>Erythrina strica</i> roxb	Papilionaceae	Hydromethanolic extract of leaves		– Inhibit xanthine oxidase (XO) activity – Decrease Hyperuricemia	[81]
<i>Rhus coriaria</i> (sumac or sumak)	Anacardiaceae	Hydroalcoholic extract of fruits	Phenolic (as gallic acid), methyl gallate and protocatechuic acid	Reduce uric acid level and have antioxidant activity	[82]
<i>Juniperus phoenicea</i>	Cupressaceae	Decoction of fresh leaves in water	Phenols	Inhibit xanthine oxidase	[58,83]
<i>Momordica charantia</i> (Bitter)	Cucurbitaceae	Methanol-water extract of pulp	Phenols and Flavonoids		
<i>Apium graveolens</i> (Celery)	Umbelliferae	Dried powdered leaves			
<i>Petroselinum crispum</i>	Umbelliferae	Parsly leaves			
<i>Linum usitatissimum</i> (Flax)	Linaceae	Seed			
<i>Cucurbita pepo</i> (Pumpkin)	Cucurbitaceae	Seed			
<i>Zingiber officinale</i> (Ginger)	Zingiberaceae	Rhizome			
<i>Curcuma longa</i> (Turmeric)	Zingiberaceae	Whole plant			
<i>Cinnamomum</i> sp. (Cinnamon)	Lauraceae	Leaves			
<i>Rosmarinus</i> sp. (Rosemary)	Labiatae	Leaves			
<i>Origanum majorana</i> Linn.	Labiatae	Ethanollic and aqueous extracts of root and stem	Phenols, flavonoids, tannins triterpenoids, saponins, polyphenols, coumarins, ellagic acid, valoneic acid dilactone	– Inhibit xanthine oxidase – Anti-gout activity	[84]
<i>Prunus cerasus</i> L. (tart cherry)	Rosaceae	Cherry juice	Anthocyanins	– Antioxidant – Anti-inflammatory	[85]
<i>Phyllanthus niruri</i> Linn.	Euphorbiaceae	Methanolic extract of plant	Lignans	– Uricosoric action – Xanthine oxidase inhibition	[86]
<i>Glycine max</i>	Leguminosae	Plant extract	Allantionase	– Release nitrogen from purine nucleotides into amino acids	[87]
<i>Arabidopsis thaliana</i>	Brassicaceae		Allantoate amidohydrolase Ureidoglycine aminohydrolase Ureidoglycolate amidohydrolase		
<i>Vinca</i> sp.	Apocynaceae	Plant extract	Vinblastine alkaloid	– Antifungal – High potential antigout – antimicrotubule	[10,88]
<i>Colchicum</i> sp.	Colchicaceae	Plant extract	Colchicine alkaloid	– Antipredator and antifungal (plant protector) – Antitubulin activity – Efficient antigout: combination of colchicine and antiurate drug	[10,89–91]

of peroxisomes in terrestrial vertebrates [94]. Uricases of most microbial and aquatic vertebrate species are soluble and remain in either the cytoplasm (bacteria) or peroxisome (yeast) [93].

Nonsense mutations caused a pseudogenization of the uricase gene in humans. Despite being non-functional, cDNA sequencing ensured that uricase mRNA is present in human liver cells and that these transcripts have two premature stop codons [95–97].

When functional uricase gene was deleted from mice, the animals died shortly after birth, while the xanthine oxidase inhibitor allopurinol prevented the deaths. The inability of mice to undergo the sudden buildup of uric acid has indicated that ancient apes

underwent successive mutations to slowly decrease uricase before pseudogenization [98]. However, other hypothesis to prevent the sudden formation of uric acid in ancient primates may be the gradual attenuation of the uricase activity before pseudogenization events [99].

In most plants, break down of purine bases gives rise to CO<sub>2</sub> and ammonia [100]. However, in root nodules of legumes, nodule bacteria incorporated the newly fixed nitrogen into purine nucleotides, then converted to allantoin and allantoic acid, which play a crucial role in the storage and translocation of nitrogen to other tissues [101,102].

Bacteria and fungi have the capacity to utilize numerous compounds, including purines, as nitrogen and carbon sources. In *Pseudomonas aeruginosa*, the encoding genes for the initial deamination step of adenine and guanine, used as nitrogen sources, are located on different loci on the chromosome, while the genes encoding the enzymes degrading hypoxanthine to ureidoglycolic acid are linked to each other [103]. Recently, it was reported that *E. coli* bears gene that encode for guanine deaminase [104] and many encoding genes involved in the purine catabolic pathway [105]. It was found that the expression of these genes was not sufficient to support growth using purines as the sole nitrogen source; however, when aspartate was added as the nitrogen source, purines could stimulate growth [105]. *E. coli* can utilize allantoin but not hypoxanthine as a nitrogen source under anaerobic conditions. The genes encoding enzymes for both allantoin and glyoxylic acid metabolisms are linked and their expressions are controlled by the *allR* gene product, when allantoin and glyoxylic acid are used as the effector molecules [106].

Fluri and Kinghorn [107] suggested that a single gene (*all2*) is involved in uricase induction and activity in *Schizosaccharomyces pombe*. Five mutants were isolated at the *a112* gene on the basis of their inefficacy to utilize hypoxanthine as a sole source of nitrogen. The mutants were found to be unable to utilize the purines adenine, hypoxanthine, xanthine, uric acid, allantoin and allantoic acid, although they could utilize urea and ammonia. The mutants appeared to be unable to produce the enzymes included in purine catabolism.

Mutant uricase enzymes derived from the uricase gene of colonies from *Bacillus subtilis* by staggered extension process (StEP) mutagenesis yielding two identical active mutant genes. The mutant uricase activity in *Bacillus subtilis* exhibits high uricase activity [108]. Many efforts have been made to make uric acid sensors using uricase (urate oxidase, EC 1.7.3.3) as a biocatalyst [109–113].

Under nitrogen-limiting conditions, genes of the hypoxanthine catabolic pathway in *Aspergillus nidulans* are induced by a globally acting protein and a pathway-specific regulatory protein [114]. Uric acid degradation required the expression of nine unlinked genes implicated in the metabolism of purine compounds [115–117].

In bacteria, fungi, insects, animals, and plants, oxidized purines, xanthine, hypoxanthine, uric acid, pyrimidine uracil, or ascorbate were transported by nucleobase ascorbate transporters (NATs) [118,119]. The only functionally characterized plant NAT-maize leaf permease 1 [118] was the high compatibility transporter of xanthine and uric acid that competitively binds but does not transport ascorbate [119].

*Arabidopsis* possesses purine permease (PUP) and ureide permease (UPS) gene families that are conserved only among plant species. The UPS family transport uracil, allantoin, while the purine permease transports xanthine and hypoxanthine [120,121]. In French bean, one UPS was found to transport allantoin [122].

Uridine monophosphate synthase and thymidine kinase are the regulatory enzymes for purine uptake. Studies using radiolabelled purins, pyrimidines and [<sup>14</sup>C] fluoroorotic acid revealed that the FOA recessive genes for “1-1/for 1-1” on chromosome 5 were unable to uptake uracil or uracil-like bases in *Arabidopsis thaliana* mutant [123].

To date, six loci along chromosome 5 of *Arabidopsis* genome were identified to encode nucleobase transporters: At5g03555 (from PRT family); At5g25420, At5g49990, and At5g62890 (from NAT family); At5g50300 (an AzgA-like transporter); and At5g41160 (from PUP family) [123,124]. The recently characterized AzgA adenine–guanine–hypoxanthine transporter of *Aspergillus nidulans* was found to have amino acid similarity to *Arabidopsis* loci At5g50300 and At3g10960 encode proteins [125]. The amino acid

sequence of the FUR4 uracil transporter of *Saccharomyces cerevisiae* (from PRT family) showed significant similarity to that of *Arabidopsis* locus At5g03555 encoded protein [123].

Hauck et al. [126] isolated a urate oxidase (UOX) mutant of *Arabidopsis thaliana* that accumulate uric acids in the tissues mainly in the embryo due to the suppression in a xanthine dehydrogenase (XDH). The UOX-mutant exhibits a severe inhibition of cotyledon development and nutrient mobilization from the lipid reserves in the cotyledons. The local defect of peroxisomes (glyoxysomes) in the cotyledon of the mature embryo causes the deposit of fatty acids in the dry seeds. Peroxisomes possess part of the purine nucleobase catabolic pathway and play a central role in the breakdown of fatty acids ( $\beta$ -oxidation) [127]. Without  $\beta$ -oxidation, seedling establishment cannot proceed and uric acid will accumulate in the embryo due to its weak mobility in lipids [126], Fig. 4.

Uric acid is transported into the peroxisomes and oxidized by urate oxidase [UOX] to hydroxyisourate, which is converted to S-allantoin by two further enzymatic reactions [128]. Humans possess a non-functional UOX; therefore, the final product of human purine ring breakdown is uric acid, which is excreted in the urine. In plants, S-allantoin breakdown results in the complete catabolism of the purine ring system in the endoplasmic reticulum, releasing CO<sub>2</sub>, glyoxylate and ammonia [129–131].

Hongoh et al. [132] cloned the gene encoding uricase of the yeast-like symbiont of the brown plant-hopper, *Nilaparvata lugens*, which shows 62% sequence identity with that of *Aspergillus flavus*. The symbiont uricase possessed all the known consensus motifs, except the C-terminal PTS-1, Ser-basic-Leu. The symbiont's uricase gene expressed in *Escherichia coli* was as active as those of plants and animals, but less active than those from other fungi.

Yang and Han [133] isolated two functionally allantionase genes, *AtALN* (*Arabidopsis* allantoinase) and *RpALN* (*Robinia pseudoacacia* allantoinase). The absence of nitrogen in the medium increased the expression of these genes. The cloned *AtALN* and *RpALN* encoding allantionase confirmed that allantoin catabolism pathway exists in both *Arabidopsis* and *Robinia* spp. Multiple sequence alignment showed that those allantoinase genes share homology with those isolated from *E. coli*, bullfrog and yeasts.

Recombinant *Hansenula polymorpha* MU200 was obtained by expressing uricase from *Candida utilis*. The highest production of recombinant uricase reached 52.3 U/mL (about 2.1 g/L of protein) extracellularly and 60.3 U/mL (about 2.4 g/L of protein) intracellularly in fed-batch fermentation after 58 h of incubation, which are much higher than those expressed in other expression systems [134].

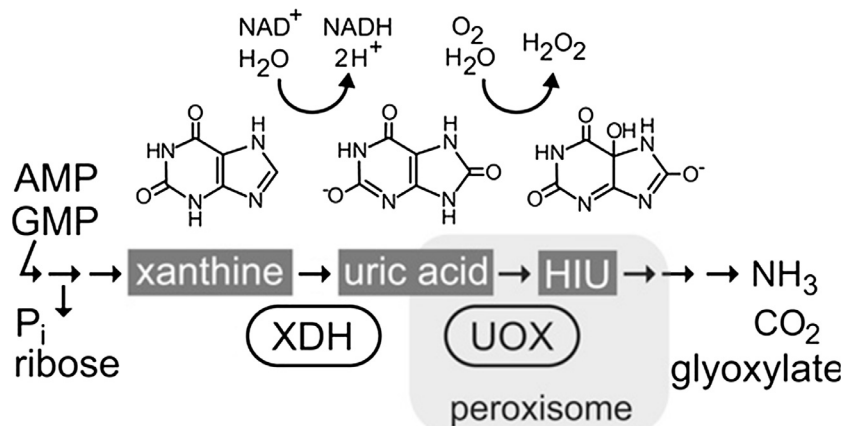
Rasburicase is a recombinant urate oxidase produced from *Saccharomyces cerevisiae* harboring *Aspergillus flavus* uricase gene. It acts as an alternative to allopurinol for reducing uric acid levels, so it has been used for the handling of anticancer-therapy-induced hyperuricemia [135].

The cloned uricase gene (UOXu) of *Candida utilis* contains 909 base pairs and encodes a protein with 303 amino acid residues and a mass of 34,1463 Da [136]. Cloned urate oxidase gene of *C. utilis* was recombined in the plasmid of the probiotic *Lactobacillus bulgaria* to produce urate oxidase that breaks down uric acid. The recombinant plasmid PMG36e-U containing urate oxidase gene of 34 KDa molecular weight has an activity up to 0.33  $\mu$ /mL [137].

Saeed et al. [138] expressed an uricolytic activity from *Escherichia coli* harboring uricase gene from *Pseudomonas aeruginosa*. The sequence of the cloned gene shows 44% similarity to the uricase gene of *Cellulomonas flavigena* and 35% to that of the yeast *Beauveria bassiana*.

Meraj et al. [139] induced mutated *Bacillus subtilis* with the ability for hyperproduction of urate oxidase using ethyl methane sulfonate at 180 min dose rate. The advantages to adopt





**Fig. 4.** Purine nucleotide catabolism based on reactions catalyzed by xanthine dehydrogenase (XDH) and urate oxidase (UOX). HIU, 5-hydroxyisourate; Pi, phosphate. Adapted from Hauck et al. [126].

mutagenesis technique for the productions of many microbial enzymes, are their simplicity and low cost. However, the cloning technique is very expensive and requires high technical facilities.

### Conclusions and future perspectives

Uric acid is a catabolic insoluble product of purine metabolism. Humans are unable to further degrade uric acid. In normal cases, uric acid is excreted with urine, but in gouty cases, longstanding elevation of monosodium urate crystal deposit in joints, kidneys and tissues, as a consequence of hyperuricemia. Until now, the future for gouty patients largely depends on whether the best ways of management for gout are widely spread, since we already have excellent standards for diagnosis and very effective chemical and herbal treatments for most patients. Unfortunately, these treatments were hampered by the less knowledge of our genetics, foods nature as well as our bad lifestyle and eating habits which reflect their repercussions on our general health.

This review article focuses on the different types of foods present in our diet in relation to uric acid levels as some dietary plant foods may be low, moderate or even high in uric acid contents. It also point out on how the different life forms (human, animals, plants and microbes) can genetically handle uric acid metabolism and catabolism. Attentions were made on the various mechanisms by which plant secondary metabolites and microbes (bacteria, fungi and actinomycetes) enzymes' degrade uric acid to soluble ammonia.

Future perspectives must be made in the way of increasing the awareness of populations to these open areas of research basing on the statement 'prevention is better than cure'. Major advances should also focus on the manufacture of recombinant probiotic microorganisms carrying uricase genes to use it in the treatment of gout in addition to the present chemical and herbal treatments.

### Conflict of interest

The authors have declared no conflict of interest.

### Compliance with Ethics Requirements

This article does not contain any studies with human or animal subjects.

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