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AN OVERVIEW OF URICOSURIC DRUGS AND THEIR SCREENING METHODS

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ABSTRACT

Uricosuric medications increase the excretion of uric acid in urine, thus reducing the concentration of uric acid in blood plasma. Prolonged and untreated hyperuricemia results into gout, a severe inflammatory condition. Crystals of monosodium urate may then form, particularly in the joints and connective tissues. These crystals initiate attacks of acute gout, and tophaceous deposits may occur if the hyperuricaemia is allowed to persist. The naturally available uricosuric agents are Tinospora cardifolia, Allium sepa, Cajanus cajan, Piper nigrum etc., Uricosuric agents increase the urinary excretion of uric acid hence the natural uricosuric agent is preferred to prevent many diseases like gout, arthritis, kidney stones etc., without side effect. The various screening methods for the uricosuric activity are uricosuric activity in mice, Potassium oxonate induced activity, Phenol red excretion method.

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INTRODUCTION

Uricosuric medications are the substances that increase the excretion of uric acid in urine, thus reducing the concentration of uric acid in blood plasma.

Prolonged and untreated hyperuricemia results into gout, a severe inflammatory condition. Sustain hyperuricemia leads to impaired blood pressure control, renal impairment and nephropathy [1]. The drugs used in treatment of hyperuricemia and for prophylaxis of gout include xanthine oxidase inhibitors viz. allopurinol and uricosuric agents like probenecid and benzbromarone [2]. Allopurinol is contraindicated in patients with compromised renal function [3] and frequently causes severe hypersensitivity reactions [4]. Febuxostat is contraindicated in liver failure [5]. Uricosuric agents furthermore can't be administered in patients with renal stones [6]. So, it is the need of the today to find out novel drug with minimal adverse effects. Hence natural medicinal plants having uricosuric activity is the best approach in treating hyperuricemia.

URATE DIPOSITION AND GOUT:

When the level of uric acid, primarily in the form of monosodium urate [7], exceeds the point of maximum solubility, crystals of monosodium urate accumulate particularly in the joints and connective tissues. These crystals initiate attacks of acute gout [8], and tophaceous deposits may occur if the hyperuricaemia is allowed to persist. While the drugs colchicine and phenylbutazone are useful in treating the acute attack of gout owing to their anti-inflammatory activity [9], the most effective approach to the long-term treatment of hyperuricaemia involves reducing the urate level so that the gouty attacks gradually cease and the deposits of urate formed during the hyperuricaemic periods are gradually resorbed. Urate levels can be lowered by decreasing the rate of production of urate or increasing its rate of elimination. With respect to the first alternative, the drug allopurinol, which blocks the conversion of hypoxanthine and xanthine to uric acid, is now in widespread use either by itself or in combination with one of the uricosurics [10]. However, the most common method of reducing urate levels is to use drugs which increase the rate of elimination of urate by the kidneys. The long and fascinating history of the development of uricosuric agents has been reviewed in detail by Gutman (1966) [11].

FORMATION OF URIC ACID:

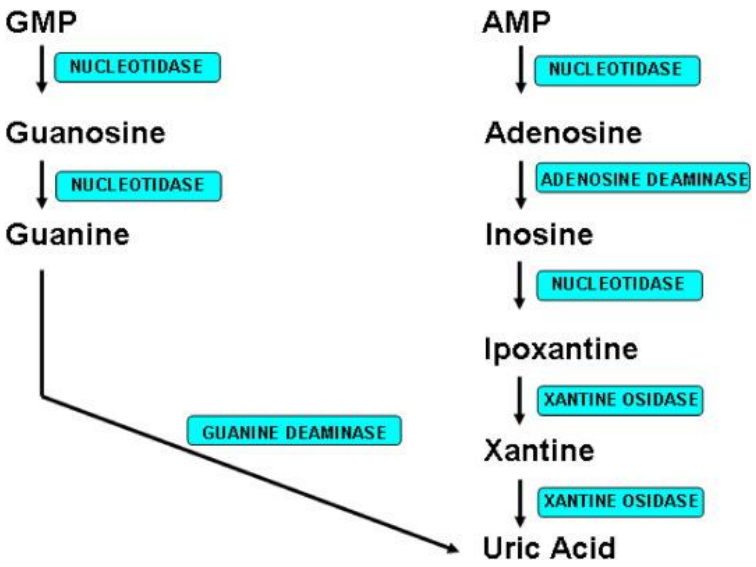

FIGURE NO: 1 Formation of uric acid.

A SHORT HISTORY:

The uricosuric properties of salicylate were noted before 1890 and its use as a uricosuric continued through the 1950s. As late as 1955, Marson [12] felt that salicylate was superior to probenecid for the long-term treatment of gout. However, for appropriate uricosuric activity, salicylate must be administered in doses greater than 5 0 g/day, often resulting in tinnitus, gastric bleeding, and many other serious side effects, so the use of salicylate as a uricosuric gradually waned. During the time that salicylate was in use, a number of other drugs were found to have uricosuric activity and were introduced for clinical use. Cinchophen (2-phenylcinchoninic acid) was introduced by Nicolaier and Dohrn (1908) [13], but its use was discontinued by the late 1940s because of its hepatotoxicity. A number of cinchophen derivatives were also tried, but all showed unacceptable side effects. In the 1940s, Beyer[14] and his associates at Merck, Sharpe and Dohme found that the drug carinamide could retard the renal excretion of penicillin, thus increasing its effective half-life in the body [14]. Shortly thereafter, it was discovered that carinamide increased the excretion of uric acid [15], and this drug was introduced as a uricosuric.

Probenecid can cause nausea, vomiting, and severe hypersensitivity reactions, and sulphinpyrazone can cause leucopenia and exacerbation of peptic ulceration. Current research is hampered in part by a relative ignorance of the mechanism of action of these drugs [16].

Herbal remedies obtained from traditional herbs and medicinal plants are commonly used in Unani system of medicine. In rural areas, health and healing are usually in the alternative form of a hand-me-down herbal concoction. Even in the developed countries, herbal vendors trade fresh plants and preparations for various conditions ranging from fever to abortifacients. There are thousands of herbal plants that folklore had attributed medicinal benefits to treat gout [17]. However, a considerable number of plants still need to be scientifically validated; hence, much work is still needed to investigate the bioactivity of these plant. Excessive production of uric acid leads to deposition of urate crystals in soft tissues and joints which is linked to gout [18]. Gout is metabolic disorder in which deposition of uric acid occurs in joints. Allopurinol is commonly prescribed to manage gout.

Xanthine oxidoreductase (XOR) is a highly versatile enzyme that is widely distributed among species (from bacteria to man) and among the various tissues of mammals. It is a member of the group of enzymes known as molybdenum-iron-sulphur-flavon hydroxylases. XOR has two interconvertible forms, xantine oxidase (XO) and xanthine dehydrogenase (XDH). Both the enzymes catalyze the oxidation of hypoxanthine to xanthine and then to uric acid, the final reactions in the metabolism of purine bases [19]. There is substantial evidence that over activity of this enzyme leads to a condition, generally called as gout [20].

URICOSURIC AGENTS:

Uricosuric drugs which increase the urinary excretion of uric acid, or XO inhibitors which block the terminal step in uric acid biosynthesis, can lower the plasma uric acid concentration, and are generally employed for the treatment of gout [21]. Allopurinol is a clinically used Xanthine oxidase inhibitor in the treatment of gout, but this drug suffers from many side effects such as hepatitis, nephropathy and allergic reactions [22]. Moreover allopurinol and its active metabolite oxypurinol is catalyzed by Xanthine oxidase itself, resulting in the generation of reactive oxygen species such as Superoxide anion (O2 -) is involved in various pathological states such as hepatitis, inflammation, ischemia, reperfusion, carcinogenesis and aging [23-24].

URICOSURIC ACTIVITY:

Synthesis of uric acid primarily occurs in the liver, but the kidney has an important role in the patho-physiology of hyperuricemic syndromes. Because uric acid is poorly soluble, excessive amounts in the circulation may precipitate out into the tissues, particularly the joints, resulting in a painful arthropathy ("Gout"). In humans these condition is usually the result of faulty tubular transport of urate, resulting in increased net reabsorption.

Reduction of net uric acid synthesis by inhibition of xanthine oxidase is the preffered therapeutic approach. Xanthine oxidase catalyzes the oxidation of hypoxanthine and xanthine to uric acid [25].

METHODS FOR DETERMINING THE URICOSURIC ACTIVITY:

The following methods were used to determine the uricosuric activity on animal models.

1. Uricosuric activity in mice.
2. Uricosuric activity after Potassium Oxonate treatment in rats.
3. Phenol red excretion in rats.

URICOSURIC ACTIVITY IN MICE:

PROCEDURE:

1. Male NMRI mice weighing 25-30g are used.
2. On the evening prior to the experiment, food but not water is withheld.
3. In the morning, the mice are orally loaded with 50ml/kg 0.9% Nacl solution.
4. Together with the sodium load the test compound is applied by gavage in 2% starch suspension. Controls receive saline and starch suspension only.
5. Groups of 5 mice are placed into metabolic cages.
6. Urine is collected over 4h. In the urine sodium and potassium are determined by flame photometry, chloride by argentometrically with potentiometrical end point titration (Chloride titrator, Aminco). Uric acid is determined by the Uriquant-method [26].
7. Creatinine is determined by the jaffe-reaction.

URICOSURIC ACTIVITY AFTER POTASSIUM OXONATE TREATMENT IN RATS:

PROCEDURE:

1. Male Wistar rats weighing 250g are placed individually in metabolic cages.
2. They are offered a special diet containing 5% fructose, 3% Uric acid, 2% potassium oxonate (2,4-dihydroxy-1,3-triazine-6-carbonic acid) and 0.001% artificial sweetener.
3. Drinking water consists of a 0.5% solution of potassium oxonate solution.
4. The treatment is repeated on the second day.
5. On the third day 24 h urine is collected and the animals are sacrificed by exsanguinations.
6. Concentrations of uric acid and electrolytes (Na^+, K^+, and Cl^-) are determined in blood and urine [27].

PHENOL RED EXCRETION IN RATS:

PROCEDURE:

1. Phenol red (phenolsulfonphthalein) excretion is an indirect test for uricosuric activity.
2. Male Wistar rats weighing 120-150g are treated orally with the test compound or the standard compound.
3. 30min prior to intravenous injection via the tail vein with 2.5ml/kg of a 3% aqueous solution of phenolsulfonphthalein for intravenous application, 5.0 ml/kg of the test drug solution are injected immediately after the phenolsulfonphthalein injection followed by flushing with 2.5ml/kg saline.
4. By retro-orbital puncture blood samples are withdrawn after 30, 60 and 180 min.
5. Blood (0.2ml) is diluted with 2ml 0.9% Nacl- solution and centrifuged.
6. To 1ml of the supernatant 1 ml of 1% sodium carbonate solution and 8 ml of saline are added.
7. Using spectrophotometer extinction at 546 nm is determined [28].

PLANTS HAVING URICOSURIC ACTIVITY [29]:

Table No: 1 Medicinal plant and their parts having uricosuric activity.

S.NO	MEDICINAL PLANT NAME	PART USED
1.	Tinospora cardifolia	Leaf
2.	Allium sepa	Bulb
3.	Barleria prionitis	Root
4.	Bauhinia variegate	Flower
5.	Brassica nigra	Seed oil
6.	Cajanus cajan	Seed
7.	Calamus rotang	Stem bark
8.	Cassia senna	Leaf, fruit
9.	Cissus quandrangularis	Stem
10.	Crataeva magna	Root bark
11.	Crinum latifolium	Leaf
12.	Crinum asiaticum	Leaf
13.	Cryptolepis buchananii	Root
14.	Decalepis hamiltonii	Root
15.	Enicostema axillare	Whole plant
16.	Gloriosa superb	Tuber
17.	Hemidesmus Indicus var.Indicus	Root
18.	Hemidesmus Indicus var.Pubescens	Root
19.	Hygrophila auriculata	Whole plant
20.	Piper nigrum	Fruit
21.	Rauwolfia serpentine	Root
22.	Rubia cardifolia	Root
23.	Tinospora cordifolia	Leaf
24.	Trewia nudiflora	Root
25.	Triticum aestivum	Fruit
26.	Tribulus terrestris	Whole plant
27.	Aerva lanata	Whole plant
28.	Boerhavia erecta	Whole plant
29.	Mimosa pudica	Whole plant
30.	Phyla nodiflora	Leaf

CONCLUSION

I would likely to take this time to summarize everything i have said in this blog regarding uricosuric activity. Uricosuric agents increase the excretion of uric acid thus reducing the concentration of uric acid in the body and increasing its rate of elimination. The medicinal plants having uricosuric activity and the screening models for uricosuric activity are explained in this activity. Therefore natural medicinal plants having no side effects are more preferred when compared to synthetic medications.

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