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Understanding the mechanism of gout in poultry and its management

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Abstract
Poultry industry is facing a huge challenge to reduce the economic losses due to gout particularly when it affects young chick in masses. Gout leads to mortality, production loss as well as carcass condemnation in birds. Significantly high serum uric acid level (hyperuricemia) in a super saturated state may get deposited in kidney or joints or may deposit over most of the visceral organs including liver, heart, lungs, thoracic wall, abdominal viscera, spleen etc. The principal patho-physiological change in the background of gout is considered either overproduction or decreased utilization of uric acid or reduced renal clearance of uric acid, which leads to hyperuricemia. The pathways leading to hyperuricemia or gout may be different but result is same i.e. excessive deposition of chalky white uric acid crystals exclusively in kidney or joints or all over the viscera. Sporadic cases of gout may be observed in all age group of birds; however, massive outbreak of gout in all its form but more importantly renal gout has been recorded in chicks and starters characterized by heavy mortality, uneven growth pattern and heavy economic loss to poultry industry. Scientists world over are in search of therapeutic agents which could help in effective management and control of clinical cases of gout especially in the face of acute outbreak. Present day approach is to take measures which could restore the healthy functioning of kidneys by way of providing vitamin A supplementation, change of feed formulations, use of toxin binders and agents which could regulate renal physiology *i.e.* nephroprotective agents. The use of xanthine oxidase inhibitors *viz*. allopurinol and febuxostat is increasingly gaining importance in poultry gout management.

Keywords: Poultry industry, birds, patho-physiological

Introduction
In India about 4 million peoples are directly or indirectly employed in poultry industry [6]. Presently, India is producing about 3.4 million tons' eggs and 3.8 million tons broiler meat annually and ranks 3rd and 7th in global egg and meat production respectively [32]. Apart from disease outbreaks, poultry gout drastically affects the health of birds and cause massive economic losses to poultry industry. Gout is an important metabolic disease of poultry, characterized by deposition of urate crystals in the body tissue because of persistent hyperuricemia (Elevated serum uric acid level). Based on location of urate deposition, gout in poultry can be classified as visceral gout, renal gout and articular gout.
This phenomenon is unique to poultry. This property of avian species is attributable to their uricotelic nature *i.e.* in poultry the major end product of nitrogen catabolism is uric acid which comprises of 70- 80% of excreted nitrogen in ureteral urine. The remaining amount consists of urea, creatinine and amino acids. This is because birds lack the enzyme uricase, which converts uric acid into allantoin [16]. It is quite evident in poultry that kidney dysfunction can play vital role in the development of gout unlike mammals in which availability of enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT) for conducting salvage pathway to recycle purine break down product. This review attempts to provide practitioners, students and researchers a detail information regarding etiology, clinical manifestation, pathogenesis, diagnosis, prevention and management of avian gout. This article does not only provide the literature review but also at the same time the knowledge and experience gained through self-research and learning activities.

Uric acid production
Nitrogenous base, Purine i.e. adenine and guanine are the precursor of uric acid and the source of purines may be endogenous as a result of cell death or it may be exogenously acquired

through feeds, particularly animal protein feed. Uric acid in birds is produced from the different body organs like kidneys, intestine, muscles, endothelial cells, however, mainly synthesized in liver and excreted via kidneys [7].

The different steps in the metabolic conversion of purines to uric acid are as follows:

- Adenosine monophosphate (AMP) is converted to inosine by removing an amino group by deaminase to form inosine monophosphate (IMP) which is then then dephosphorylated to form inosine with the help of nucleotidase. This process can also be achieved by nucleotidase which first form adenosine by removing a phosphate group and then inosine by process of deamination.
- Enzyme nucleotidase is needed to convert Guanine monophosphate (GMP) to guanosine.
- Later, the nucleosides, inosine and guanosine, are converted to hypoxanthine and guanine, respectively. The reaction is metabolized by help of enzyme purine nucleoside phosphorylase (PNP).
- In penultimate step, xanthine-oxidase (XO) oxidizes Hypoxanthine to xanthine and while guanine is deaminated to form xanthine by help of guanine deaminase.
- In the final step, uric acid is formed from xanthine with the help of terminal enzyme, xanthine oxidize.

Xanthine oxidase (XO) is the rate-limiting enzyme in purine catabolism. Terminal reactions needed for conversion of xanthine into uric acid is mediated through xanthine oxidase, with simultaneous reduction of NAD^+ or O_2. This enzyme uses O_2 as final electron acceptor, therefore, electrons bind unstably to oxygen forming hydrogen peroxide (H_2O_2) and superoxide anion ($O\cdot^-$). These oxygen derived free radicals produced by XO, finally leads to toxicity of body cells [5].

Etiology of gout

Gout in poultry may be due to infections, nutritional imbalance, toxicity or impaired renal functions that it is of multifactorial origin. As uric acid is excreted through kidneys, 70% of the kidney dysfunction is attributed to formation of hyperuricemia and gout. High sodium bicarbonate, copper sulfate, Calcium and Vitamin D3 with low phosphorus in the feed, high amount of salt (more than 0.3 percent) intake, feed containing more than 30 percent of protein, less water intake can result in hyperuricemia. Viral infection causing nephropathy like avian nephritis, astrovirus, Infectious Bursal Disease are among the important causes. Injudicious use of antibiotics like gentamycin, nitrofurosones etc. or poisoning of feed by disinfectants like cresol and phenol, can all be other causes of hyperuricemia and thus gout [10, 32].

Infectious causes

The common viruses involved in the pathogenesis of gout are the nephro-pathogenic infectious bronchitis virus (IBV), avian nephritis virus, infectious bursal disease virus (IBDV) and recently the chicken astrovirus has been reported to be involved in gout in commercial broilers in India.

In India the most common Infectious bronchitis virus (IBV) reported since 1991 are the Mass (GenBank accession number HM179146) and 793B types [11]. Bayry *et al*., [1] isolated the nephro-pathogenic IB Virus from the kidney samples of gout affected chickens. From 2010 onwards, the scenario in India has changed as vaccination against nephro-pathogenic IBV in broiler breeder flocks is carried out and cases has dropped. However, once again in 2011, due to uncertain reasons, the outbreaks of gout were observed in India.

Avian astrovirus infection is again a leading cause of gout and thus affecting Indian poultry industry [18]. In India, Avian Nephritis virus (ANV) and chicken Astrovirus (CAstV) are two prevailing types that have been recognized. ANVs not only affect kidneys but also causes enteritis and therefore, were first isolated from rectal contents of the broiler chicks [14]. In chicks manifestation varies from subclinical to outbreaks of runting stunting syndrome and chick nephropathy [30]. Bulbule *et al*., [4] reported several outbreaks of gout in broilers in India in the year 2011–2012 causing about 40% mortality in birds. From 80% of these cases, Astrovirus were detected. Although, mixed infection (ANV + CAstV) or (ANV+CAstV+IBV) are being found now a days, where the level of detection of CAstV predominates on ANV and IBV. No cases were found to be affected alone with ANV or IB Viruses.

The acute symptomatic manifestations of Infectious Bursal Disease Virus (IBDV) was observed in a flock of 14 and 15 week old chickens and at necropsy, apart from lesions on bursa of Fabricius, the kidneys appeared to be somewhat swollen and mottled [17]. Ingrao *et al.* (2013) [13] discussed the complex host-pathogen interaction in Infectious Bursal Disease (IBD) and revealed that in addition to the BF being principal diagnostic organ, on post mortem examination of birds that died during the acute phase of vvIBD, dehydration and nephrosis with swollen kidneys were the common findings.

Non-infectious causes

One of the important factors attributed for the incidence of visceral gout is the percentage of dietary calcium in the broiler starter ration. BIS (1992) have given different standard specifications as maximum inclusion of 1.2 per cent. The excess of dietary calcium for a long period causes damage to kidney and parathyroid gland in young chicks and older poultry as reported by [3].

Feizi *et al.* (2012) [12] reported that inclusion of 2 per cent calcium in broilers diet lead to some disorders in the physiologic process of kidneys consequently resulting in urate deposition on serous surfaces of viscera, especially kidneys that are the main lesion of gout syndrome that causes heavy mortality in flock.

Few studies have associated aflatoxicosis with gout, hyperuricemia. Fungi, *Aspergillus flavus* is the source of Aflatoxin. This mycotoxin though primarily being a hepatotoxic, possess potent nephrotoxicity as well. High concentration of sodium chloride increases susceptibility of chickens to aflatoxicosis [13], however, NaCl is itself a potent nephrotoxic. Even intake of one ppm of aflatoxin produced degeneration changes in kidneys tubules and splenomegaly [24]. Broiler chicken fed with 1 ppm of aflatoxin for 6 weeks showed mild to moderate degree of tubular epithelial degeneration with the collections of mononuclear cells along with heterophils in the kidneys [21].

Pathogenesis of gout

Hyperuricemia leads to precipitation of monosodium urate crystals in kidney, joints and visceral organs. The exact mechanism of deposition or the predilection for certain site is not yet fully explored. One possible explanation has been given as lower temperature at predilection sites. Gout in general is regarded as a sequel of severe renal function disorder in poultry. The tissue damage brought about by hyperuricemia in renal parenchyma might have affected the

circulatory system with resultant passive hyperemia. This would have brought down the temperature, which in turn would have precipitated the urate crystals. Another possibility for development of visceral gout could be that a plasma urate concentration that is slightly above the solubility of sodium urate may lead to urate precipitation in the body. Those areas where the solubility of sodium urate is lower than other area constitute the predilection site. Lower temperature reduces the solubility quotient of urate and favours precipitation of urate, which grows with time to produce tophi.

In renal gout, urate crystals precipitate in the tubules or collecting ducts of the kidney or ureter. It results into acute obstructive uropathy. It may result into anuria or oligouria, which severely hinders the tubular secretion of uric acid. This leads to significant rise in serum uric acid level within a short span of time. A vicious cycle is formed with progressive hyperuricemia and precipitation of urate at predilection sites, terminating into death.

In avian species, the excretion of uric acid not only occurs through kidneys but also through the digestive tract. Urinary tract contributes about 75% excretion while the rest 25% is excreted through the digestive tract. ABCG2 is a gene transporter for UA in the SLC17A3 genes and impaired function of the transporter ABCG2 leads to decreased excretion of uric acid through the GIT resulting in rise of serum levels of uric acid and enhanced renal excretion. In the kidneys uric acid excretion process involves: glomerular filtration followed by reabsorption in the proximal tubules. A part of the reabsorbed UA is secreted in interstitium, with another reabsorption phase in the proximal tubules. At the end only 10% of the filtered urate is excreted, while the rest is reabsorbed back into the circulation [2].

Uric acid crystals being insoluble requires Urate transporter1 (URAT1) and the organic anion transporters, OAT1 and OAT3, to help cross cell membranes [20]. Transporter URAT1, on the kidney tubules are encoded by SLC22A12 gene. URAT1 transports uric acid through the proximal tubules into the tubular intersitium by active transport process. Polymorphism of these genes, therefore, results in diminished excretion of uric acid. Uricosuric drugs such as probenecid, sulfinpyrazone, benzbromarone etc. decreases URAT1 activity, and affects uric acid reabsorption in proximal tubules. Pyrazinamide, nicotinate and lactate like drugs increase glomerular filtration and urate reabsorption from the interstitium into the kidney tubules by augmenting the acting on URAT [18]. Some other genes responsible for serum uric acid levels include the SLC2A9, SLC17A3 and SLC22A11, glucokinase regulatory protein (GCKR), Carmil (LRRC16A), and PDZ domain containing 1 (PDZK1) genes [23].

Types, Clinical Signs and lesions

Based on location of urate deposition, gout in poultry has been classified as: [a] Visceral gout (where urate deposits are seen on one or multiple visceral organs as well as on the peritoneal surface or thoracic wall), [b] Renal gout (in which urate crystals are mainly deposited in renal parenchyma) and [c] Articular gout (in which deposition of urate crystals are observed in synovial surface of tarso-metatarsal joint as well as in hip joint). In visceral gout, kidneys tubules are distended with urate crystals shows brittle white staghorn calcium urate calculi. Urate deposits are seen on one or multiple visceral organs as well as on the peritoneal surface or thoracic wall. In articular form, urate deposition develops on synovial membrane of tarso-metatarsal joint as well as in hip joint and wing joint and incite a granulomatous reaction [19]. It is also being stated that factors like synovial pH, water and electrolytes level or some other components in the synovium such as proteoglycans and collagen may affect the solubility of uric acid in the joint [20]. Others factors such as low temperature in the joints also decreases the solubility of urates, thus increasing the incidence of articular gout, however, this concept needs to be more clarified and why in majority of cases peripheral joints are involved is still unknown.

The broilers having average serum uric acid level of about 9.05 mg/dl did not develop signs of visceral gout, which indicates that in broiler clinical gout may not develop if the levels of serum uric acid stay below 10mg/dl [28]. This is in contrast to mammalian biochemical parameter to assess renal dysfunction. In mammals, serum creatinine level is considered best option to assess renal dysfunction as compared to estimation of blood urea and serum uric acid[9]. Increase in the level of aspartate aminotransferase, alanine transaminase and Superoxide dismutases in the serum are also seen in affected birds [28].

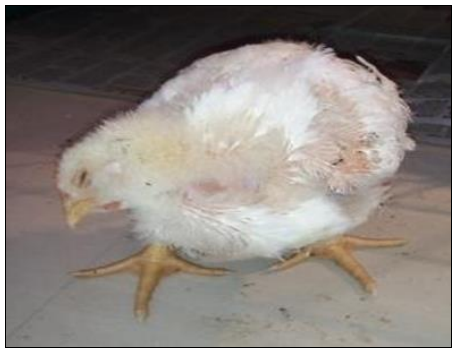

Fig 1: Showing dullness and depression in a gout affected chicken

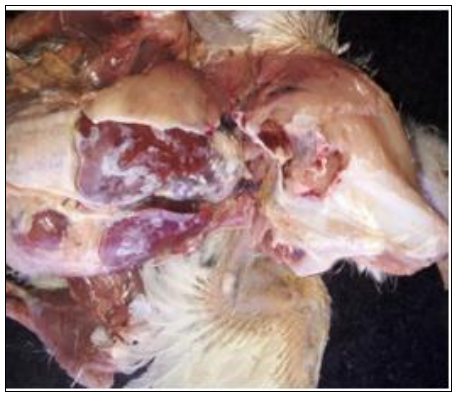

Fig 2: Showing deposition of chalky white deposits over the visceral organs during necropsy examination a bird

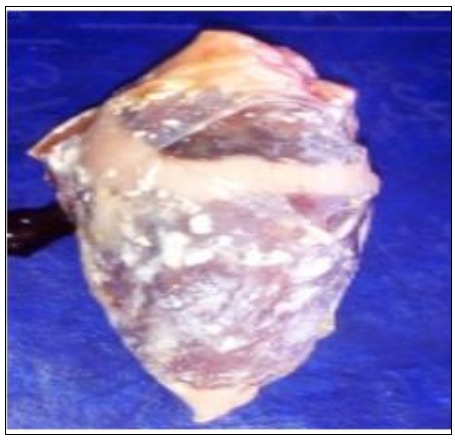

Fig 3: Chicken heart showing pericardium with severe urate deposits

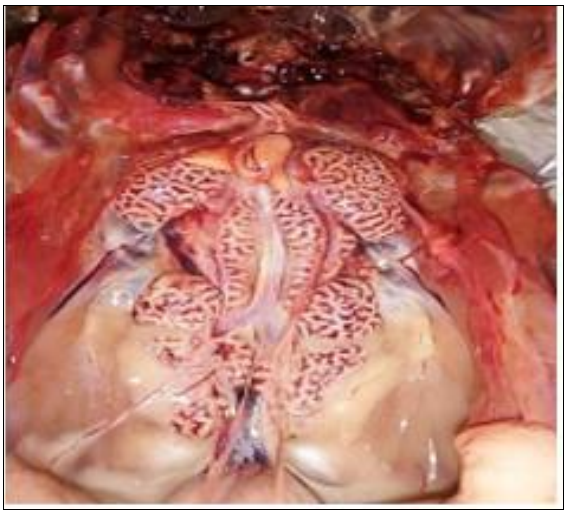

Fig 4: Chicken kidney showing distended ureters with urate deposit

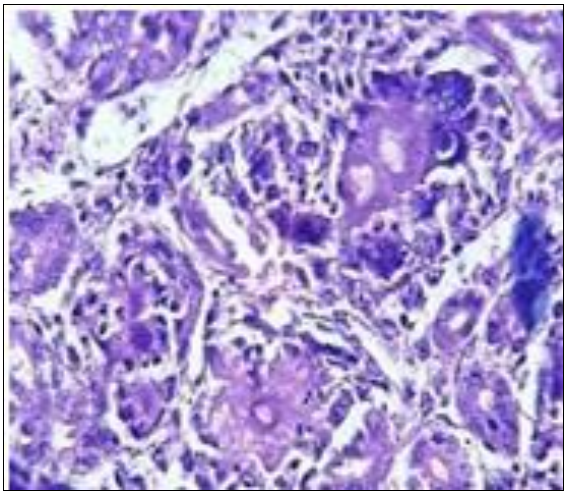

Fig 5: Photomicrograph of affected Kidney section showing acicular urate crystals deposition with degenerative changes in renal tubules (H&E, 10X)

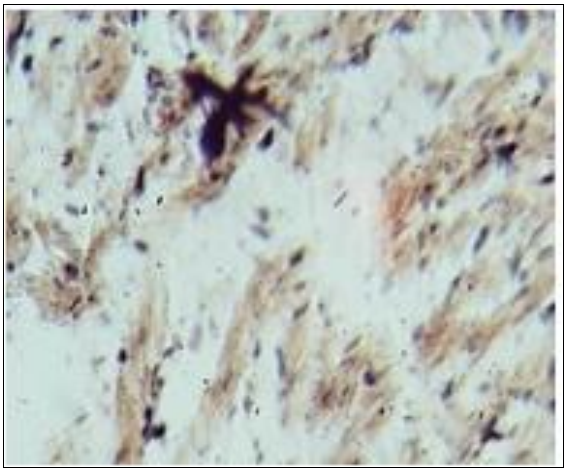

Fig 6: Photomicrograph showing acicular shaped urate crystal in heart section. (DeGlantha, 40X)

Ultra-structural pathology revealed abundance of electron dense uric acid bodies. These bodies were distributed randomly in the cytosol as well as lining the nuclear or organellar membranes. Another interesting feature observed ultrastructurally in gout affected birds was disruptive changes in the mitochondrial membrane, mitochondrial cristae, nuclear membrane (which showed characteristic bleb formation) and presence of swollen microtubules [28].

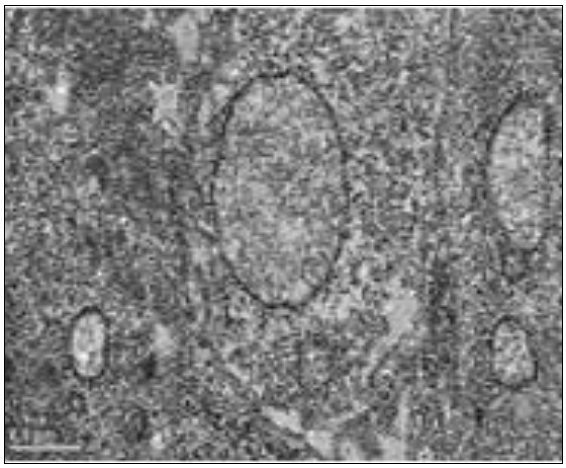

Fig 7: Ultrastructural view of kidney showing presence of electron dense uric acid crystals in both cytosol and perinuclear membrane in gout affected birds. (×4000).

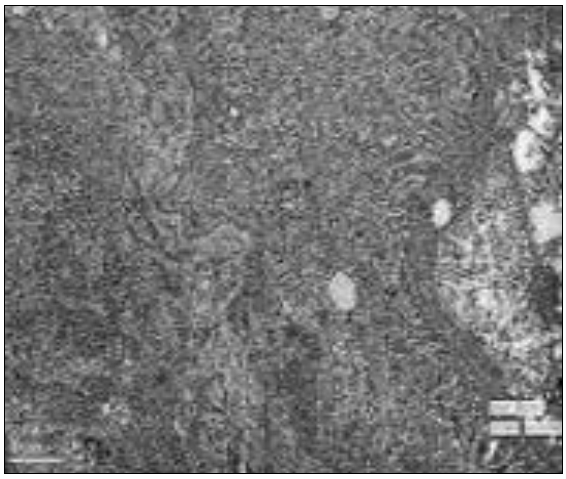

Fig 8: Ultrastructural view of kidney showing swollen microtubules in kidney of gout affected birds. (×2550).

Diagnosis

Diagnosis of avian gut could be made through obtaining complete history, signs and symptoms, lesions during post mortem examination of dead birds. The symptoms of dullness, dehydration, soiled vent with whitish pasty droppings, reluctant to move, swollen and painful joints are all indicative of gout in birds. Urate deposits are white and semi solid and must be differentiated from yellow fibrinous or purulent inflammatory exudates. Macroscopically, the aspirated material from articular gout looks like toothpaste. The presence of urate can be performed by murexide test, where a small amount of nitric acid is mixed with little quantity of suspected material on a slide. It is then, dried by evaporation in a flame and allowed to cool. Development of mauve colour on addition of small drop of conc. ammonia, confirms urate crytals. Microscopically, dark coloured acicular crystals can be seen in smears of tophi, when special staining is done using De Glantha stain. It helps to demonstrate urate crystals, which appears as sharp needle shaped tophi. A polarizing microscope is helpful in identification. Determination of uric acid concentration includes HPLC, biosensor methods, phosphotungistic acid methods and uricase methods [25].

Management

Gout in poultry often occurs sporadically in adult birds and does not warrant persistent therapeutic measures. However, in

young chicks between 1-3 weeks of age it may affect majority of the birds in the flock. In such cases, once the disease has been confirmed, it becomes imperative to take curative measures immediately. The current scenario has necessitated searching ways and means to control the progress of hyperuricemic state by exploring agents which could reduce the level of serum uric acid in poultry as well as reverse the pathological process which has brought about nephropathic changes, so that normal renal function is restored without affecting any other organ-system of the body.

It becomes a major challenge for veterinary professionals to control the episodes of gout in poultry. The counter measures available to treat cases of gout are very limited and often inadequate. Two important aspect needs to be covered in deciding therapeutic regimen are:

1. Lowering of the uric acid level by use of anti-gout medications along with which nephroprotective medicine needs to be given to normalize the renal function in birds of the flock.
2. In addition, as per requirement anti-viral medicine/measures for viral etiologies and antimycotoxic measures such as use of toxin binder or change of feed is usually being recommended.

Change of feed, provision of adequate water and supplementation of vitamin A only helps in checking the progression of disease but does not bring about reversal of tissue damage to state of health. In addition, medicines are required to counter the inflammatory conditions may be by providing steroids. The ultimate way is to lower the serum urate level and dissolve the crystal deposits either by enhanced elimination by uricosuric agents like *probenecid, benzbromarone, sulfinpyrazone, A*cidifying the urine with ammonium chloride or ammonium Sulphate or reducing the formation of uric acid by xanthine oxidase like allopurinol and febuxostat.

Poultry professionals are arbitrarily using allopurinol and febuxostat as over the counter medication. Allopurinol is a xanthine oxidase inhibitor drug, which not only decrease formation of uric acid but also helps in the dissolution of uric acid crystals due to which further progression of chronic gouty arthritis is prevented. The concentration of increased plasma uric acid is taken down and further precipitation is stopped leading to gradual disappearance of formed urate acid crystals. After the development of marked kidney dysfunction, allopurinol fails to restore renal function but may slow progression of condition [29]. On the other hand, Febuxostat is a non-purine-selective inhibitor of xanthine oxidase and works by non-competitively blocking the molybdenum pterincenter. Molybdenum pterincenter is the active site on xanthine oxidase. Hence, febuxostat reduce production of uric acid by inhibiting xanthine oxidase [22]. In a study conducted, it was concluded that both allopurinol and febuxostat carries good ameliorative potential as an anti-hyperuricemic and anti-gout agent in broiler grower birds. However, febuxostat showed better ameliorative potential as compared to allopurinol. However, at higher doses a potential for development of nephrosclerosis was evidenced in allopurinol treated birds characterized by formation of reticulin fibers in renal interstitium evidenced ultra-structurally, while Febuxostat showed hepatotoxic potential as well as potential for progressive fibrosis and chronic hepatotoxicity [26, 27]. At therapeutic level, both allopurinol and febuxostat were tolerated well by broiler grower birds. Hence, it should be judiciously used in proper dosage for better therapeutic outcome.

Conclusion

An attempt has been made to review the literature from available works done on poultry gout along with the experience gained through research programme and working experience. Gout is an extremely important metabolic disease of great economic importance in poultry industry. The principal patho-physiological change in the background of gout is considered either overproduction or decreased utilization of uric acid or reduced renal clearance of uric acid that leads to hyperuricemia. Nephropathy remains the basic cause of gout and the causes may be infectious or non-infectious. Scientists world over are in search of therapeutic agents which could help in effective management and control of clinical cases of gout especially in the face of acute outbreak. Recent introduction of two important anti-gout agents used in human medicine can be a better option to control and treat the cases of gout in birds.

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