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Review Article

BIOCHEMICAL ROLE OF XANTHINE OXIDOREDUCTASE AND ITS NATURAL INHIBITORS: AN OVERVIEW

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ABSTRACT

Xanthine oxidoreductase (XOR) is a widely distributed housekeeping enzyme in mammals that catalyzes the last two steps in human purine catabolism to produce uric acid. The enzyme exists as a homodimer with independent electron transfer in each monomer. This has been studied extensively as a major constituent of the milk fat globule membrane (MFGM) which surrounds fat globules in cow's milk even though purine catabolism is the most accepted function of XOR. A huge number of literature highlights on the different catalytic forms of XOR and their importance in the generation of reactive oxygen species/reactive nitrogen species (ROS/RNS) and synthesis of uric acid which are involved in many physiological and pathological processes. However, a slight ambiguity resides in their biochemical functions. The aim of this article was to review the literature published on the structural, catalytical, physiological and pathological role of XOR and to resolve the ambiguity in biochemical processes and to firm up various natural inhibitors of XOR collectively. Uric acid, the product of purine catabolism shows antioxidant activity, and XOR-derived ROS and RNS play a role in innate immunity, milk secretion and also be involved in signaling and metabolism of xenobiotics. Furthermore, XOR is likely to be engaged in pathology because of excessive production of uric acid and ROS/RNS. This review also reports natural XOR inhibitors in plants which inhibit the enzyme to treat XOR associated pathology.

Keywords: Xanthine oxidoreductase, Housekeeping enzyme, Purine catabolism, Hyperuricemia, Allopurinol, XOR natural inhibitors

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INTRODUCTION

Xanthine oxidoreductase (XOR) is a widely distributed enzyme which has been extensively studied for more than 100 y because of its abundance in bovine milk which is available on a large scale. Bovine milk XOR is the first studied enzyme [1]. XOR has been isolated from different species from bacteria to men, yet minor structural and catalytical differences found in different species [2-5]. XOR is a truly representative form of two enzymes i. e xanthine dehydrogenase (XDH; EC 1.1.1.204) and xanthine oxidase (XO; EC 1.1.3.22). They represent two forms of the same gene product. Mammalian XOR is synthesized in XDH form but converted to XO through irreversible post-translational modification in the presence of various stimuli [3, 6-8]. Merely mammalian XOR exists as two forms, whereas other species contains only the XDH form.

This property is an added advantage to mammals to study XOR as an evolutionarily conserved housekeeping enzyme [6]. It is a well-studied enzyme with a huge number of biochemical functions which plays a major role in physiology and pathology of humans. However, many review papers have been published on structural, physiology, pathological, and catalytic mechanisms of this enzyme, several questions yet to be answered to resolve ambiguity in the interconversion of XDH to XO and its influence on biochemical activities. Present review mainly focused on resolving ambiguity with respect to interconversions and their influence on principal biochemical activities and also outlined the natural inhibitors of these enzymes.

Molecular structure and pathway of electron transfer in XOR

XOR is a molybdenum-containing enzyme belongs to XO family. All the enzymes of this family possess multiple iron-sulfur clusters (at least two) in addition to the molybdenum center and FAD. Mammalian XOR is a homodimer consisting of two independent subunits with a molecular mass of 145KDa [6, 9-11]. Each subunit consists of one molybdopterin (MO-pterin) unit, two un-identical non-sulphur redox centers (Fe/SI and Fe/SII) and FAD as cofactor distributed in the C-terminal (85 KDa), N-terminal (20 KDa) and intermediate (40 KDa) domains respectively [9, 12-13]. Members of the XO family of enzymes usually catalyzes the oxidative hydroxylation of carbon center of their substrates typically aromatic heterocyclic's or aldehydes. In this mechanism Mo (VI) is reduced to Mo (IV) at the active site [2]. This follows the oxidation of fully reduced XOR molecule includes the transfer of its six electrons to acceptor [14, 15]. Usually the substrate binds to the active site positioned nearer to molybdenum domain from there electrons transfers to acceptor through iron-sulfur proteins and flavin adenine dinucleotide (FAD) respectively [16]. Electron transfer is independent in two independent subunits [2].

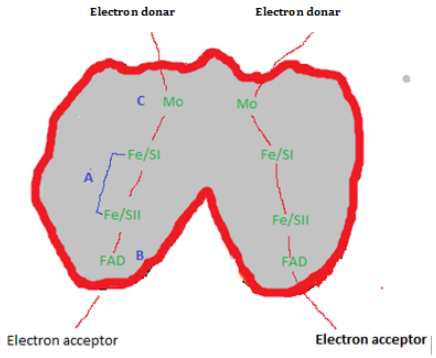

Fig. 1: Inverted butterfly catalytic structure and electron transfer pathway of XOR dimer: Each XOR monomer includes A. N-terminal domain (20-kDa) B. Intermediate domain (40-kDa) C. C-terminal domain (85-kDa). The pathway of electron flow in XOR includes an MO-pterin unit, two unequal iron–sulfur redox centers Fe2/S2I and Fe2/S2II) and one molecule of FAD respectively [reviewed in 2, 14]

In the fig. [1] Electron donors are of same substrates, but electron acceptor is different in two forms of the enzyme. In XDH, nicotinamide adenine dinucleotide (NAD^+) is the preferred acceptor and in case of XO form oxygen (O_2) is the electron acceptor which

can produce superoxide anion, hydrogen peroxide (H_2O_2) which acts as an important signaling molecule and also has a potential to generate reactive oxygen species (ROS) but in intermediate form XOD which was produced because of reversible thiol oxidation of XDH can reduce both NAD^+ and O_2 [15, 17-18]. The intermediate form can also produce ROS because of O_2 reduction.

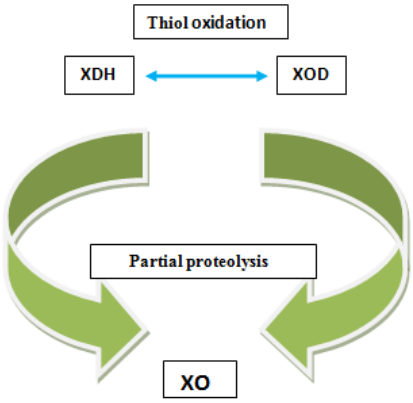

Fig. 2: Biological interconversions of mammalian XOR: Thiol oxidation converts XDH into reversible XOD (intermediate form) of the enzyme. Partial proteolysis converts XDH and XOD into the irreversible XO form [reviewed in 15, 17-18]

Recently NADH oxidase activity of an enzyme has been identified where NADH donates its electrons directly to FAD to an electron acceptor O_2 [19]. And also some papers have reviewed nitrates reducing power of XOR especially XO form. XO can reduce inorganic nitrates, glyceryl nitrates to nitric oxide (NO) under hypoxic conditions in the presence of NADH or xanthine as a reducing substrate which acts as an important signaling molecule. Moreover, in the presence of O_2, superoxide reacts rapidly with NO to generate reactive nitrogen species (RNS) particularly peroxynitrite an even more powerful bactericidal agent [17, 20-21]. A further complication is that this reaction can affect vasodilation effect of NO particularly in the ischemic conditions of vasculature when NO synthase activity is low. In this context, the two enzymes can be seen as complementary [22].

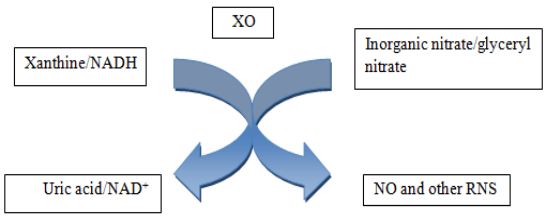

Fig. 3: Reduction mechanism of nitrates by XO: Xanthine/NADH donates electrons to nitrates and oxidizes to uric acid/NAD^+. Nitrates accept the electrons and reduces to NO and other RNS

Distribution of mammalian XOR

In mammals, XOR has been distributed in many organs; however highest levels are found in the liver, intestine and biological fluids such as blood, milk [23-26]. In respect of humans, highest levels are found in liver, intestine [27-31] while a very low activity has been detected in other organs [32-33]. Interestingly, human endothelial cells from the microvasculature of several tissues have been reported as expressing high levels of XOR activity [34]. XOR can be found in human milk and blood, but activity is low compared to bovine milk and blood under physiological conditions, but it can be increased under pathological conditions. [5, 35-37].

Biochemical roles of XOR

Being a widely distributed enzyme XOR has been involved in many biochemical functions. These functions play a major role in physiology and pathology.

Physiological role of XOR

The physiological involvement of XOR is potentially complex. Although normal cellular/tissue distributed enzyme has an affinity for several substrates including aldehydes, purines, pyrimidines, pteridines, aza purines, heterocyclic compounds and retinol [35, 38] but the conventional role is purine catabolism especially in the liver [9, 15]. Despite purine catabolism other housekeeping functions of XOR are detoxification of xenobiotics, including antiviral and anticancer agents and regulation of cellular redox potential, lactation [6, 39, 40]. First three reactions involve in the generation of ROS/RNS, which are crucial to physiological functions such as innate immune defense and signal transduction.

Purine catabolism

In normal physiological conditions, XDH form of the enzyme was predominant in tissues and catalyzing the oxidative hydroxylation of hypoxanthine to xanthine and the oxidation of xanthine to uric acid. Uric acid acts as a potent antioxidant and free radical scavenger necessary to protect a cell from oxidative damage caused by ROS and RNS [9, 15, 19, 41]. This has been the proposed reason for increased lifespan in humans. Therefore, the lack of uricase activity could represent an evolutionary advantage for uricotelic primates over ureotelic mammals [42-43].

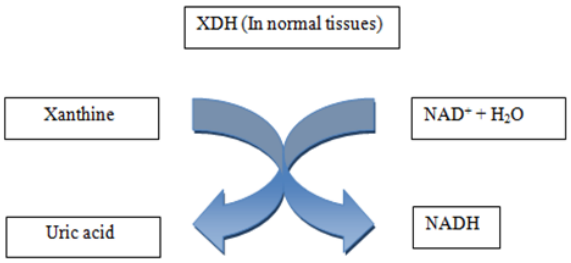

Fig. 4: Mechanism of action of XDH: Xanthine donates electrons to NAD^+ and oxidizes to uric acid. NAD^+ accepts the electrons and is reduced to NADH in normal tissues

Purine catabolism has also been detected in epithelial cells and vascular endothelial cells, but uric acid is secreted on the surface of these cells expanding their role extra in nasal fluid, saliva, and other body fluids as a systemic antioxidant [44-47].

Innate immune defense

Surprisingly XOR itself contributes the synthesis of numerous ROS and RNS in XO form. In the early 1980s hypothesized that XDH can be converted to XO in the presence of stimuli (cell and tissue injury). This property of XOR to rapidly convert from XDH to XO makes XOR an ideal component for a fast immune response [6, 48].

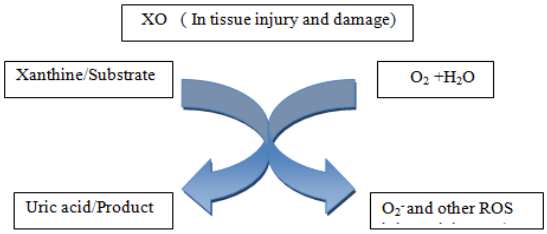

Fig. 5: Mechanism of action of XO: Xanthine/other substrate donates electrons to O_2 and oxidizes to uric acid/other substrates. O_2 accepts the electrons and reduces to O_2^- and other ROS

From last two decades, attention has been focused on the ability of the XOR to generate ROS/RNS. At lower levels these two acts as secondary messengers, but at higher levels, they have an antimicrobial action which plays a major role in the cellular innate immune activity [49-51]. In addition to ROS/RNS uric acid the product of purine catabolism also plays a major role in immune defense mechanism as an antioxidant and free radical scavenger, besides being an anti-inflammatory effector with numerous protective roles in the body. The protective functions are not only at the cellular level but also involved in systemic functions due to circulating XOR and serum uric acid [47, 52-53]. Circulating XOR is in XO form due to proteolysis by plasma proteases [54]. Healthy mammals have low levels of circulating XOR. In the case of humans, these levels can dramatically increase in response to a range of diseases, particularly those affecting the liver [18]. XOR has been implicated as a destructive agent, particularly in many forms of ischemic-reperfusion (IR) injury due to the production of ROS/RNS [6, 16, 41, 55]. Nevertheless, the cytotoxic properties of ROS/RNS can also be beneficial, and an antimicrobial role for bovine milk XOR has been considered for many years. XOR initiates an antimicrobial response in response to infection, cytokines or other pro-inflammatory mediators. These stimulate XDH to XO conversion which leads to the generation of ROS, and neutrophil infiltration inflammatory response. The neutrophils then act to combat the infectious agents [56-58]. Further examples of antimicrobial action of XOR identified in GIT, bile duct, vascular endothelium resulting from the generation of ROS and RNS. XOR also plays a major antimicrobial role in the bile juice produced from the lining of bile ducts [6, 40].

Recently new hypothesis were proposed to explain the antimicrobial property of milk. The location of XOR on the surface of fat globules in milk is well suited to its proposed antimicrobial role of mammalian milk. It is still an area of research how the purely structural role of XOR in secretion relates to the proposed antimicrobial function. It is most likely to be hypothesized that the pathogenic bacteria which can be targeted epithelial membrane antigens of the digestive tract are likely to bind to similar antigens on MFGM [59]. This interaction probably brought into close contact with XOR which is present on MFGM reinforced by the enzyme affinity for acidic polysaccharides, present on many bacterial capsules [60]. This interaction could be the stimulus for conversion of XDH to XO to generate ROS [61]. Still, it is not clear which is reducing substrate for the XO. This aspect is being under active area of investigation. XOR derived H_2O_2 exerts its antimicrobial effects by acting as a substrate for the lactoperoxidase system in milk.

$$\text{Unknown substrate} + O_2 + H_2O \rightarrow \text{Unknown product} + O_2^- \text{and other ROS}$$

In view of the newly discovered role of XOR to reduce nitrite to NO in the generation of RNS particularly peroxynitrite, can be seen as a potential mechanism of antimicrobial activity of milk. Usually, nitrate concentrations are likely to be high in the immediate micro-environment of enteric bacteria favoring XOR-catalyzed reduction to NO.

Signal transduction

As discussed above in innate immune defense at low levels XOR-generated ROS/RNS act as secondary messengers in signal transduction, but convincing proof of the involvement in cellular signaling yet to be ambiguous. Recently a new hypothesis described the location of XOR on the outer surface of cultured human endothelial and epithelial cells, and to be localized to surfaces opposed to those of closely neighboring cells which are involved in cell-cell interactions [62].

In addition to above prominent activities, an XOR-generated ROS are responsible for Iron mobilization from ferritin in the liver [63], iron absorption in the intestinal mucosal [64] and the induction of proliferation [65-67]. It was also postulated that free radical generation by XOR and various metabolic pathways in developmental animals believed to be influenced the development [3].

Role of XOR in lactation

Recently, evidence has been reported for the involvement of XOR in milk secretion [68]. XOR occurs in the milk fat globule membrane (MFGM). Fat droplets originate in the endoplasmic reticulum of the mammary secretory cell. In the secretion process, they migrate to the luminal surface and bud off from the cell, enveloped by the apical cell membrane to form a MFGM [61, 69]. Immediately after leaving the cell, the fat droplet is surrounded by a true biological membrane. During this process, the enzyme moves from the cytoplasm of the secretory cell to the apical cell membrane where it combines with adipophilin and butyrophilin. XDH was shown to form a complex with these proteins which mediate coupling between lipid droplet and the apical plasma membrane in the secretion process. This activity depends only on its protein structure not owing to catalytic activity.

Regardless of many decades of research into XOR, the human enzyme has characterized recently. The catalytic activity of human liver XOR is similar to bovine milk [70] enzyme, but surprisingly human milk enzyme has low xanthine oxidase activity due to its low molybdenum content (less than 5%). The NADH oxidase activity of human milk XOR is essentially same as that of the bovine milk enzyme which involves only FAD site [71]. The low enzymatic activity of human XOR is a puzzle [72]. If the process of milk secretion does not require enzymatic activity, this is only necessary in the first few weeks postpartum, in order to fulfill an antimicrobial role in the neonatal gut. Thereafter, this requirement ceases, and the activity falls to the level commonly found in purified milk XOR, which is generally obtained several weeks after birth. It was also reported that goat and sheep milk enzymes have relatively low activity similar to human XOR which has molybdenum contents of 9% and 18% respectively.

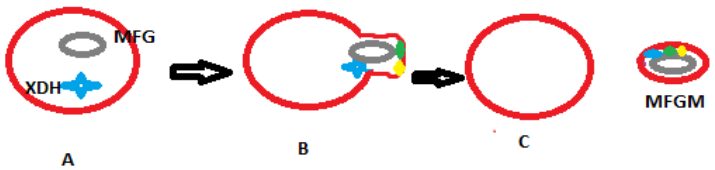

Fig. 6: Structural role of XOR in milk secretion process of mammary secretory cell

A. Fat droplets originate in the endoplasmic reticulum of the mammary secretory cell and XOR movement from the cytoplasm of the secretory cell to the apical cell membrane B. Migration of fat droplets to the luminal surface enveloped by the apical cell membrane to form a MFGM [61, 69] and combining of XOR with adipophilin and butyrophilin on apical cell membrane C. XDH mediates coupling between lipid droplet and the apical plasma membrane in the secretion process.

Pathological role of XOR

So far several hundreds of publications have published about the involvement of XOR in pathogenesis, although the specific pathogenic mechanisms are still debated [41]. Whatever may be the mechanisms the agents involved in pathogenesis are ROS/RNS and uric acid generated by XOR.

Role of ROS/RNS in pathology

The usual function of ROS/RNS as a destructive agent has been illustrated in 1986 in IR injury [73]. IR injury is cell death that commonly results from interruption of blood flow to specific tissue, which occurs in a myocardial infarction or stroke. It can represent an unusual response to sequence a normal physiological process in

the vasculature, namely inflammation. On the basis of their studies of feline intestinal ischemia, Granger and colleagues proposed the consequences of events. In the course of ischemia, the energy status of the cell falls, transmembrane ion gradients break down, and the levels of intracellular calcium increase, which leads to activation of a calcium-dependent protease that irreversibly converts XDH into the XO. Concomitantly, cellular ATP is catabolized to hypoxanthine, which accumulates. On reperfusion, oxygen again becomes available and is reduced by the hypoxanthine-XO system, generating superoxide and H_2O_2. These ROS then interact to generate hydroxyl radicals with consequent oxidation of biological molecules, including proteins, lipids, and nucleic acids. This process directs to tissue injury which plays a major role in respiratory and cardiovascular disease. This mechanism also has been considered to be a reason for the difficulty in organ preservation for transplantation, particularly for XOR-rich organs, such as the intestine and liver. Therefore, the University of Wisconsin preservation solution includes allopurinol although XOR activity was not definitively shown to be the main source of oxidative stress in tissue grafting [74].

As well as in vascular pathology, the exocytosis of XOR upon cellular insults/stress, such as ischemia has been recognized to be a component in the pathogenesis of reperfusion injury [75-76]. In addition, several studies have suggested that circulating XOR can bind to vascular endothelial cells, thus providing a center of attention for oxidative stress/damage at sites far from the initial injury [75, 77].

During the 1970s and early 1980s, a new hypothesis was promoted to explore an association between cows' milk XOR and ischemic heart disease [78, 79]. In this context, produced anti-bovine MFGM antibodies might cross-react with platelet membrane antigens, inducing platelet aggregation and hence atherogenesis. However, this hypothesis was later disproved, and it can be argued that they were anti-XOR autoantibodies and their role is protective, serving to remove endogenous XOR arising from various pathological states. Their elevated levels in myocardial infarction (MI) patients could be in response to enzyme released from vascular endothelial cell lesions [79].

Role of uric acid in pathology

Hyperuricemia is the most cited pathology caused by XOR. It is a pathological condition caused by several reasons including over production by XOR, underexcretion, renal tubular disorders of uric acid. A hyperuricemic state possibly will also develop following tumor cell necrosis producing the so-called "tumor lysis syndrome" as neoplastic cells leak purines into the interstitial fluid and plasma, potentially leading to renal failure [80-81]. Congenital diseases may also give rise to hyperuricemia; the two most common are Lesch-Nyhan and Kelley-Seegmiller Syndromes–X-linked recessive disorders involving the overproduction of uric acid owing to complete or partial lack of hypoxanthine guanine phosphoribosyl transferase (HGPRT) in elevated concentrations of XOR substrates in the cell [80, 82-83]. Hyperuricemia condition follows various pathological changes. Even though most frequently expressed clinical condition was gout with the deposition of uric acid crystals, particularly in the joints, giving rise to rheumatic problems such as dysarthria it may develop other insignificant pathologies such as urolithiasis/nephrolithiasis, chronic kidney diseases, and cardiac disorders also [84-85].

So far discussion carried about XOR physiological activities, its association in pathology. In addition to this, deficiency of xanthine oxidase due to a genetic defect or severe liver deficiency has been detected. Hypouricemia, increased excretion of hypoxanthine and xanthine are associated with xanthine oxidase deficiency [86].

Inhibition of XOR

The most commonly prescribed drugs for hyperuricemia of any cause is allopurinol, which has been a central part of clinical therapeutics for over 60 y. Allopurinol is converted to oxypurinol (also xanthine) in the process of inhibiting XOR, and is a competitive inhibitor of xanthine that actually inactivates the enzyme. It remains the only commercially available inhibitor of XOR in the United States [87]. Many recent studies have focused on natural and synthetic inhibitors of XOR that might be used as part of a daily regimen or be used to replace or synergize with allopurinol because of severe side effects of allopurinol [87-89]. Possibly the most promising synthetic pharmaceutical is known as TEI-6720 or Febuxostat [87, 90-92]. This compound is not a competitive inhibitor of XOR but instead interfere at the active site as a stably bound/docked molecule. It was proposed to be safe in patients with renal failure, but the evidence is not yet available [93-94].

In spite of the wide use of synthetic analogs in the treatment of gout the search for novel XO inhibitors with fewer side effects and potent activity are essential not only for the treatment of gout but also treat other diseases associated with the XO activity. In this review, we tabulated the various natural XO inhibitors that have been identified.

Table 1: List of natural XO inhibitors and IC_{50} values

Plant name	Part/extract	Active phyto constituent	IC_{50} value of µg/ml or) µm/ml	Reference
Silybum marianum	Sylimarin extract	Silibinin	27.58+/-3.48	[95]
Tephrosia purpurea	Methanolic root extract	Polyphenols, Flavonoids	-	[96]
Erythrina indica	Methanolic stem bark extract	Flavonoids	52.75	[97]
Erythrina stricta	Chloroform fraction	-	21.2	[99]
Cranberry	Juice	-	2.4	[99]
Purple grapes	Juice	-	3.5	[99]
Black tea	Extract		5.8	[99]
Green tea	Dried leaves	Epigallocatechin gallate (EGCG)	0.48	[100]
Japanese knotweed	Root	Resveratrol	-	[100]
Origanum syriacum	Aqueous extract of aerial parts	-	317	[101]
Origanum vulgare L	Aqueous extract of aerial parts	-	403.9	[101]
Hyoscyamus reticulatus	Aqueous extract of aerial parts	-	12.8	[101]
Achillea fragrantissima	Aqueous extract of Aerial parts	-	179.9	[101]
Daphne linearifolia	Aqueous extract of aerial parts	-	-	[101]
Hibiscus sabdariffa	Aqueous extract of calyx	-	-	[101]
Aristolochia maurorum	Aqueous extract of aerial parts	-	-	[101]
Citrullus colocynthis	Aqueous extract of seed	-	-	[101]
Laurus nobilis	Aqueous extract of leaves	-	-	[101]
Pimpinella anisum	Aqueous extract of fruit	-	300.4	[101]
Tecoma stans	Ethanol extract	-	38.97	[102]
Cassia fistula	Methanol seeds extract	Flavonoids	11.07	[103]
Conyza bonariensis	Methanol extracts	Syringic acid Takakin 8-O-glucuronide	500+/-41 170+/-12	[104]
Koelreuteria henryi	Acetone extracts	-	91.8±1.7	[105]

Prunus campanulata	Acetone extracts	-	64.6±5.8	[105]
Rhodiola rosea	Acetone extracts	-	56.0 0±1.0	[105]
Aronia melanocarpa	Berries,bark extract	Anthocyanins	-	[106]
Oroxylum indicum	Seed extract	Oroxin B, oroxinA, baicalin, baicalein	-	[107]
Scutellaria baicalensis	Root	Baicalin, wogonin, baicalein	-	[108]
Cinnamomum cassia	Methanol extract of twig	-	18	[109]
Chrysanthemum indicum	Methanol extract of flower	-	22	[109]
Lycopus europaeus	Methanol extract of leaves	-	26	[109]
Polygonum cuspidatum	Water extracts of rhizome	-	38	[109]
Semecarpus Anacardium	Ethyl acetate fraction of seeds	Tetrahydroxymentoflavone	92	[110]
Lagerstroemia speciosa	Aqueous extracts of leaves	Valoniec acid and ellagic acid	-	[111]
Cyathea spinulosa	Tree	Caffeic acid	-	[112]
Salvia mitiorrhiza	Roots	Lithospermic acid	-	[113]
Palhinhaea cernua	Ethanolic extract of club moss	1-apigenin-4-(2-o-p-coumaroyl)β-d-glucopyranoside	23.95±0.43	[114]
Cinnamomum osmophloeum	Essential oil from leaves	Cinnamaldehyde	16.3	[115]
Momdica charantia	Aqueous extract	coumarin	-	[116]
Vicia faba	Plant extracts	Polyphenolic compounds	40-135	[117]
Lotus edulis	Plant extracts	Polyphenolic compounds	55-260	[117]
Chrysanthemum sinense	Methanolic extracts of flowers	Acaacetin 7-0-(3-0-acetyl) β-d-glucopyranoside	0.13-2.31	[118]
Caulerpa species	Seaweed	Caulerpenyne	-	[119]
Lonicera hypo-glauca (lh)	Ethanolic extract	Bioflavonoid and lonicera flavone	35.2	[120]
Teucrium polium	Methanol, chloroform, ethyl acetate extracts	Proanthocyanidins, gallic acid,catechin and epicatechin	0.07-11.76	[121]
Tephrosia purpurea	Root extracts	Polyphenols and flavonoids	-	[122]
Chrysanthemum coronarium	Methanol extract	-	199.5	[123]
Achillea biebersteinii	Methanol extract	-	360.0	[123]
Rosmarinus officinalis	Methanol extract	-	650.0	[123]
Ginkgo biloba	Methanol extract	-	595.8	[123]
Helianthemum ledifolium	Methanol extract	-	-	[123]
Majorana syriaca	Methanol extract	-	-	[123]
Mentha spicata	Methanol extract	-	-	[123]
Populus nigra	Methylene chloride-methanolic extracts	-	8.3	[124]
Betula pendula	Methylene chloride-methanolic extracts	-	25.9	[124]
caryophyllus aromaticus	Ethanolic extract	-	5	[124]
Hypericum perforatum	Ethanolic extract	-	50	[124]
Fistulina hepatica	Methanol extract	-	-	[125]
Hypholoma fasciculare	Methanol extract	-	-	[125]
Infundibulicy begeotropa	Methanol extract	-	-	[125]
Tricholoma populinum	Methanol extract	-	-	[125]
Eucalyptus deglupta	-	-	44.5	[126]
Syzgiumma lacense	-	-	51	[126]
Olive	Leaf extract	Secoiridoidoleuropein and other apigenin derivative	53.0	[127]
Cinnamomum cassia	Methanol extract of the twig	-	18	[128]
Polygonum cuspidatum	Rhizome extract	-	38	[128]

XO-Xanthine oxidase

All natural inhibitors extracted from specific plants collectively belongs to large groups of chemical constituents includes flavonoids, terpenoids, essential oils, polyphenols, glycosides anthocyanins and others. In addition to these plants, majorities of medicinal plants were previously reviewed [8, 129-132].

CONCLUSION

The capability of the multifunctional enzyme XOR to execute various biochemical reactions owing to the synthesis of antioxidant uric acid and generation of ROS/RNS makes it an outstanding intra and extracellular protective housekeeping enzyme and an important component of the innate immune system. XOR is involved in numerous features of mammalian innate immunity such as antimicrobial activity in various regions due to the generation of ROS/RNS and also play a major role in the oxidative defense because of the synthesis of uric acid by purine catabolism. Apart from defense, an XOR-derived ROS/RNS have multiple potential roles, in both intra-and extracellular signaling.

Additionally, the role of the enzyme in the process of milk secretion has long been suspected and recently convincingly demonstrated.

The structural role of XOR protein, rather than an enzymatic activity in milk secretion is unexpected.

XOR is also involved in pathology due to the generation of ROS/RNS and synthesis of uric acid. Moreover, ROS and RNS have the capacity to combat infection and to promulgate injury throughout the vascular system. Similarly uric acid has the capacity to act as an antioxidant and at high concentrations able to cause hyperuricemia. For these reasons the levels of the enzyme are subject to rigorous control by the associated autoantibodies, a rare example of beneficial autoimmunity.

Finally, the disease burden of hyperuricemia, which majorly involves in gout remains a major problem and increasing day by day. The available synthetic XO inhibitors are typically used to treat gout or to reduce serum levels of uric acid, yet they are exhibiting a huge number of side effects. Hence the research has been focused on natural XO inhibitors, which could have therapeutic potential in selected groups of patients with gout. However, much of the information concerning structure, catalytic mechanism and biochemical functions and also various natural inhibitors cited in this review is truthful.

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CONFLICT OF INTEREST

Self-financed. No conflict of interest

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