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The Dual Role of Xanthine Oxidase in ROS Production and Inflammation: A Focus on Novel Inhibitory Strategies

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ABSTRACT

The enzyme responsible for converting xanthine into uric acid is xanthine oxidase. This enzyme plays a key role in purine metabolism by catalyzing the oxidation of hypoxanthine to xanthine and subsequently transforming xanthine into uric acid. Xanthine has two classes one X.oxidase and X.dehydrogenase. Enzyme are responsible for the formation of free radicals in our body and this free radical cause oxidative stress and further more complications. This article covers the formation of free radical due to XOR and discuss about the potent xanthine oxidoreductase which are responsible cut down the supplies of free radicals. A newly developed series of triazole-linked isatin-indole-3-carboxaldehyde hybrids, influenced by the febuxostat framework and its binding interactions, were thoughtfully designed and synthesized as prospective xanthine oxidase inhibitors. Whereas, all of xanthine inhibitors **A19** showed the most inhibitory effect on xanthine (**IC_{50}=0.37µM**). During SAR, substitution of (OCH_3) methoxy at 5^{th} position will leads to the most accommodating for inhibitory potential.

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Introduction

Xanthine oxidoreductase (XOR) is mostly present in karyotic even pro-karyotic organelles. Mainly enzyme is belonging preserved lineage of molybdo-flavoenzymes (*M. Terao et al.*, 2016). There are two forms one is Xanthine xanthine dehydrogenase and another is oxidase (*Nelson and Handler, 1968*; *Hart et al., 1970; Bray et al., 1975*).

ROS shows to play important role in triggering of inflammasomes, particularly the NLRP3 inflammasome. This activation resulted in the maturation and release of interleukin-1β (IL-1β) and interleukin-18 (IL-18), Both are highly potent cytokines that drive inflammation. (*Harijith et al., 2014).*

Several diseases were associated with inflammation and ROS, leading to chronic conditions such as atherosclerosis. In this disease, ROS contributed to the oxidation of low-density lipoprotein (LDL) particles. Additionally, ROS-induced endothelial dysfunction promoted vascular inflammation and atherogenesis. Chronic inflammation driven by ROS could lead to DNA damage, thereby promoting mutations and tumor development *(Ranneh, Y., et al., 2017).*

A compound had been identified as the most effective inhibitor. As SAR indicated, the inhibition was largely attributed to a two-carbon spacer separating isatin and triazole., as well as methoxy substitution at the fifth position of the isatin nucleus. **A19** demonstrated potential for improvement As a xanthine oxidase antagonist. Furthermore, **caffeic acid phenethyl ester (CAPE)** exhibited the strongest xanthine oxidase inhibition along with notable free radical-scavenging activity in a study on C6-C3 phenylpropanoids. CAPE inhibited DPPH radicals by 73.93 ± 3.24% and demonstrated an **IC_{50} of (6.26 ± 1.60 µM**) against the xanthine oxidase, highlighting its potential as a strong XO inhibitor and protective agent against ROS.

This article is organized into various sections. Section **1** discusses about xanthine enzyme and formation ROS. Section **2** presents the review of mechanisms linked to inflammation. Section **3** describes the chronic disease caused due to inflammation. Section **4** proposed of deep learning model for Novel Xanthine Oxidase Inhibitors. Besides, Finally, conclusions are made in Section **5.**

Xanthine Oxidase and Reductase

The complex flavo enzyme xanthine oxidoreductase (XOR) is located in the membrane of fat globules and contains molybdenum. Xanthine oxidase (XO; EC: 1.2.3.22) and xanthine dehydrogenase (XDH; EC: 1.1.3.204) have a molecular weight of 300,000 Da and can differentiate into two distinct forms (*Nelson and Handler, 1968; Hart et al., 1970; Bray, 1975).* The xanthine dehydrogenase form is the only one that can reduce nicotinamide adenine dinucleotide (NAD+), although both forms have been shown to be capable of reducing oxygen. The same gene is known to produce both XO and XDH, and their composition of subunits and associated cofactors. requirements are comparable (*McManaman and Bain et al., 2002).*

Two ferredoxin proteins, each molecule contains a single molybdenum atom and one flavin adenine dinucleotide (FAD) molecule (Fe2-S2) groups are present in each of the enzyme's subunits. Furthermore, 1330 amino acid residues are present in each subunit (*Hart et al., 1970; Bray et al., 1975*).

Xanthine is typically initially synthase in it dehydrogenise form and is readily transformed into XO form through proteolysis or sulfhydryl group oxidation. It is said that using XOR is more accurate, even though phases of the enzymes X. dehydrogenase and X. Oxidase are known and used as XOR (*Harrison et al., 2006).*

It exhibits a broad distribution in mammalian tissues in addition to being present in all mammalian milks that have been studied to date. It is most prevalent in the kidneys, liver, and intestinal mucosal layer. The primary source of this enzyme is milk. (*Massey et al., 1969*; *Page et al., 1998; Murray et al., 2004; Fox and Kelly et al., 2006).*

The final two phases of purine catabolism during its metabolism are catalyzed xanthine oxidoreductase, which is the enzyme that limits the rate of purine catabolism. When the enzyme metabolize conversion of hypoxanthine to xanthine, it produces free radicals, which are reactive oxygen species like hydrogen peroxide and superoxide radicals. Meatbolism are also take place during conversion of urate from xanthic base. Since humans lack the urea oxidase enzyme, the reaction's final product is uric acid *(Granger et al., 1986; Metinyurt et al., 2003).*

X.oxidoreductase recognized that is activated in vivo in response to bacterial infections and exhibits antibacterial activity when hypoxanthine is present. The presence of the enzyme in breast milk can also

be explained by its bactericidal function. Thus enzyme are also responsible for protection in elementary canal in infants. *(Tubaro et al., 1980; Kenan and Patton et al., 1995; Metinyurt et al., 2003).*

In ischemia reperfusion (IR), the cytosolic calcium ion (Ca2+) concentration rises as a result of the reduction of cellular energy demand brought on by ATP breakdown in hypoxic tissue. Ca2+ or Ca2+ calmodulin-dependent proteases are activated by an increase in intracellular Ca2+. The primary XOR form present in tissues under physiological conditions, XDH, is partially proteolyzed by these proteases to produce XO *(Granger et al., 1986; Metinyurt et al., 2003*).

After ATP is broken down, hypoxanthine builds up in the cells at the same time. Superoxide and hydrogen peroxide are produced in large quantities during the reperfusion phase by tissues' elevated levels of hypoxanthine, molecular oxygen (O2), and XO. Tissue damage is another effect of these free radicals (*Granger et al., 1986; Coetzee et al., 1990*).

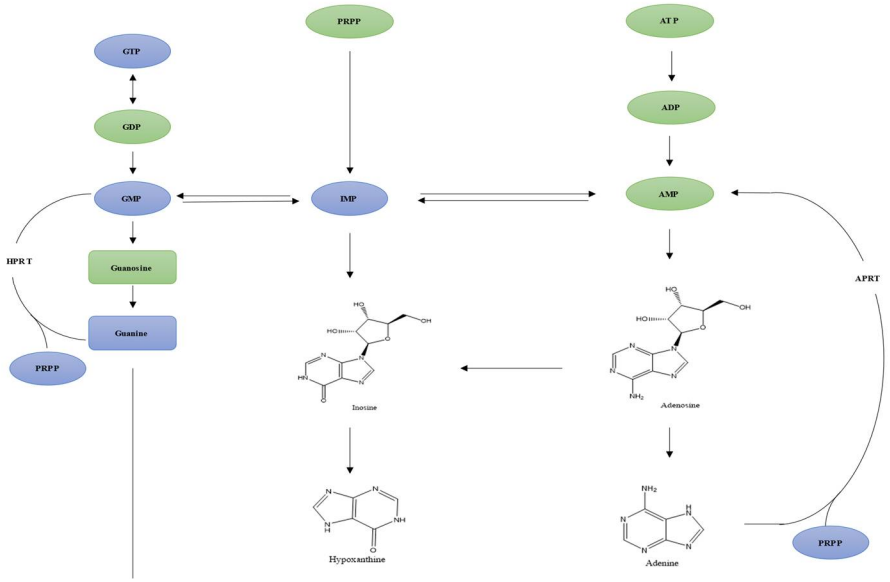
When blood uric acid levels rise too high (hyperuricemia), a form of arthritis known as gout develops. A rare condition called hypouricemia is linked to either increased or decreased urate synthesis excretion. Genetically xanthine oxidase deficiency, injurious renal disease, and liver disorders like Wilson's disease, cystinosis can all result in hypouricemia *(Onat et al., 2006).*

Recovering the active enzyme extracted from the reaction mixture for subsequent use is technically challenging due to the instability of many enzymes and the high cost associated with their purification. *(Polaina and MacCabe et al., 2007).*

However, it is known in the literature to be highly effective in solving problems because of immobilization, which protects catalytic activity and physically binds or imprisons enzymes cannot cause any free radical production and protect body from various disorders (Cabral and *Kennedy et al., 2000; Dekker et al., 2000).*

One of the main free radicals, ROS, can cause oxidative stress by starting a metabolic chain reaction when it is produced in excess. One of the main systems that influences the production of active oxygen metabolites that have a detrimental impact on cells and tissue is xanthine oxidase. It has been demonstrated that strong XO activities promote the production of superoxide, carcinogenesis, and cell death *(Dement'ev et al., 2013).*

The xanthine oxidase is crucial for illnesses, intercourse, and nutrition in mammals. In certain illnesses, such as ischemia-reperfusion in both humans and animals, reactive oxygen species (ROS) are highly active. Because of this, latest research will calculate the enhancement of bounded and unbound enzyme and identify possible antagonist of enzyme, which plays a restrictive role in purine metabolism. Although ROS are crucial for cell signaling and defense systems, oxidative stress—which is linked to



the etiology of several inflammatory diseases—can result from their overproduction or insufficient elimination.

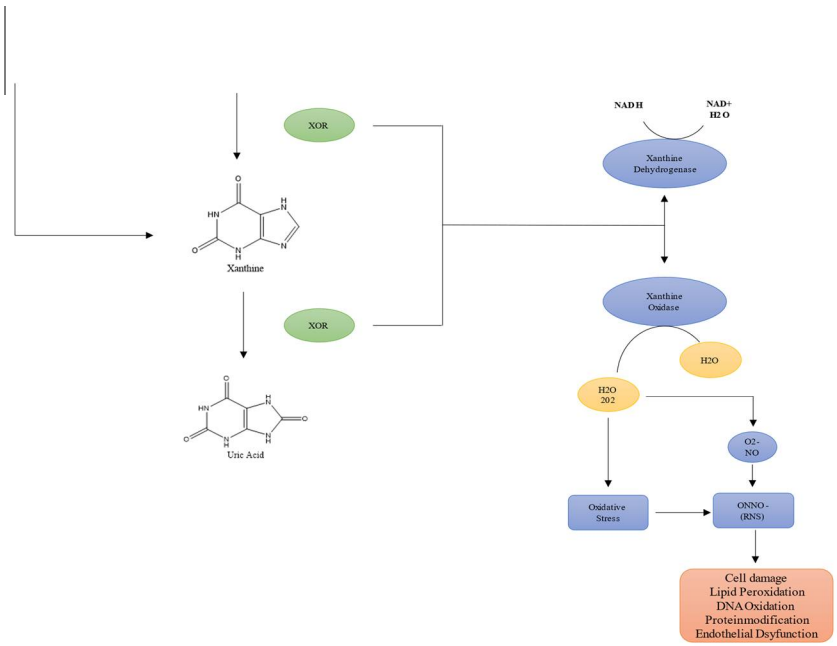


Figure 1 Represents the PRPP to uric acid with the help of XOR and leads to formation reactive oxygen species which will follow up to number of dysfunctioning like Cell damage, Lipid Peroxid', DNA Oxid', Protein modification and leads to number of diseases

Mechanisms Linking ROS to Inflammation

Explores the interconnected roles of ROS and markers that promote inflammation in the progression of chronic diseases. The authors highlight how excessive ROS production, due to environmental stressors or metabolic dysregulation, leads to oxidative stress, which in turn activates various signalling pathways, such as NF-κB and MAPK. These pathways stimulate the action of inflammation mediators (TNF-α, IL-6, and IL-1β), forming a feedback loop that exacerbates inflammation.

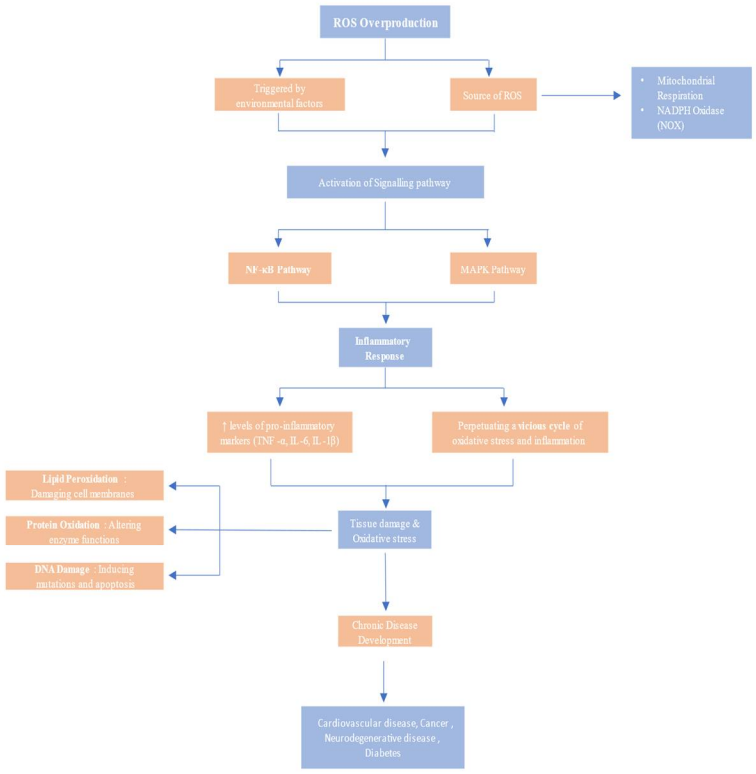


Figure 2 This pathway highlights the complex interplay between ROS and pro-inflammatory markers, emphasizing their pivotal role in promoting oxidative stress, chronic inflammation, and subsequent tissue damage. Together, these interconned mechanisms

The persistent imbalance between ROS and antioxidant defenses contributes to tissue damage and the progression of chronic conditions, including cardiovascular diseases, diabetes, neurodegenerative disorders, and cancer. The review underscores the importance of targeting both ROS and inflammatory

pathways to mitigate disease progression, suggesting that antioxidants and anti-inflammatory agents could serve as therapeutic strategies. The authors also emphasize the complex interplay between ROS and inflammation, where ROS can both promote and be a by-product of inflammatory processes *(Ranneh, Y., et al 2017)*

Chronic Disease are caused due to Inflammation

Cigarette smoke, environmental pollutants, and infections are significant contributors to chronic obstructive pulmonary disease (COPD), primarily through their role in elevating ROS phases in the lungs. Excessive ROS production triggers oxidative stress, which stimulates the release of pro-inflammatory mediators such as tumor necrosis factor-alpha (TNF-α), interleukin-8 (IL-8), and leukotrienes. These mediators drive chronic inflammation, airway remodeling, and tissue destruction, ultimately impairing lung function. The role of antioxidants in counteracting oxidative stress has been widely studied in COPD. *(Rahman, I., et al., 2006)*

Neurodegenerative Disorders

Neurodegenerative disorder, Alzheimer's and Parkinson's, are closely linked to ROS-induced oxidative stress. In Alzheimer's disease, ROS accumulation leads to neuronal damage via lipid peroxidation and mitochondrial dysfunction. Amyloid-β plaques exacerbate oxidative stress, fueling neuroinflammation and accelerating neurodegeneration. Similarly, in Parkinson's disease, dopamine metabolism generates ROS, damaging dopaminergic neurons and activating microglia, which perpetuate inflammation. These processes highlight ROS's pivotal role in the pathogenesis of neurodegenerative disorders. *(Stefanis, L., et al., 2013)*

Inflammatory Bowel Disease (IBD)

Diseases like Crohn's disease and ulcerative colitis exhibit excessive ROS production due to microbial imbalances and immune dysregulation within the gut. Elevated ROS levels cause oxidative damage to intestinal epithelial cells, weakening the mucosal barrier and aggravating inflammation. This exacerbates the clinical symptoms and progression of inflammatory bowel diseases (IBD), underscoring the need for therapeutic strategies targeting oxidative stress. *(Rezaie, T., et al., 2007)*

Psoriasis

Psoriasis is characterized by elevated ROS levels in keratinocytes, which activate inflammatory pathways, including NF-κB and STAT3. These pathways drive the generation of pro-inflammatory cytokines like IL-17 and TNF-α, leading to keratinocyte hyperproliferation and chronic inflammation. The interplay between inflammatory signaling and oxidative stress is a critical factor in the pathogenesis of psoriasis. *(Zhang, W., et al., 2016)*

Asthma

In asthma, ROS play a critical role in exacerbating airway inflammation by increasing the sensitivity of airway cells to allergens. ROS also activate eosinophils and mast cells, driving chronic inflammation and airway remodeling. This highlights the contribution of oxidative stress to asthma pathophysiology and the potential benefits of antioxidant therapies. *(Rahman, I., et al., 2006)*

Systemic Lupus Erythematosus (SLE)

Systemic lupus erythematosus (SLE) involves excessive ROS production, which damages DNA and forms neo-antigens. These neo-antigens trigger autoimmune responses, leading to chronic inflammation through the activation of cytokines like interferon-alpha (IFN-α) and TNF-α. The role of oxidative stress in driving immune dysregulation underscores its significance in SLE pathogenesis. *(Perl, A., et al., 2013)*

Non-Alcoholic Fatty Liver Disease (NAFLD)

Oxidative stress from mitochondrial dysfunction is a key factor in the development of non-alcoholic fatty liver disease (NAFLD). Excessive ROS production exacerbates lipid peroxidation in hepatocytes, activating inflammatory pathways like NF-κB and inflammasomes. This progression leads to non-alcoholic steatohepatitis (NASH), which is marked by liver inflammation and scarring. *(Buzzetti, E., et al., 2016)*

Cardiovascular Diseases (CVD)

ROS contribute significantly to the development of cardiovascular diseases by inducing endothelial dysfunction and promoting vascular inflammation. Excessive ROS production stimulates smooth muscle

cell proliferation and foam cell formation, contributing to atherogenesis and plaque instability. Chronic oxidative stress is a common feature in hypertension, atherosclerosis, and myocardial infarction. *(Madamanchi, N. R., et al., 2005)*

Chronic Kidney Disease (CKD)

In CKD, excessive ROS production damages renal cells and activates pro-inflammatory cytokines such as transforming growth factor-beta (TGF-β) and interleukin-6 (IL-6). This cascade drives fibrosis and worsens kidney dysfunction, emphasizing the role of oxidative stress in CKD progression. *(Oberg, B. P., et al., 2004)*

Obesity

In obesity, adipose tissue becomes hypoxic, leading to increased ROS production. ROS stimulate the secretion of pro-inflammatory adipokines, including TNF-α and IL-6, which play a role in chronic systemic inflammation. This oxidative-inflammatory axis plays a critical role in obesity-associated diseases, including metabolic syndrome and type 2 diabetes. *(Keaney, J. F., et al., 2003)*

Novel Xanthine Oxidase Inhibitors: Structure-Activity Relationships and Molecular Docking Insights

During recent designed and synthesized a set of new triazole-linked isatin-indole-3-carboxaldehyde hybrids designed around the febuxostat framework and also studied the molecular docking interactions and its bind site interaction as well, with respect to the inhibition of xanthine oxidase activity. Among the whole series of the compound **A19** showed the most effective inhibition against the xanthine oxidase enzyme with a calculated IC_{50} value of 0.37µM. According to the structure activity relationship methoxy (OCH_3) which is substituted at the fifth position of the isatin core and a two-carbon distance linked isatin and the triazole is highly bearable for the potent xanthine oxidase inhibition. Also, the compound **A19** showed appreciable molecular docking studies with a dock score of −35.5484 dock score having a ΔG value of −23kJ/mol as febuxostat binding sites. Furthermore, molecular docking studies also included the various amino acids residues given in **figure 3**.

Based on the structure-activity relationship, the structure's xanthine oxidase inhibitory activity is most appropriate for methoxy (OCH_3) substitution at the fifth position of the isatin core and a two-carbon

spacer between the isatin and triazole groups in addition, to having such strong xanthine inhibition action, **A19** allowed a significant amount of room for improvement on the aromatic moiety of the indole nucleus, making it a promising candidate for the creation of stronger and safer xanthine oxidase inhibitors (*Singh Atamjit et al.,2022).*

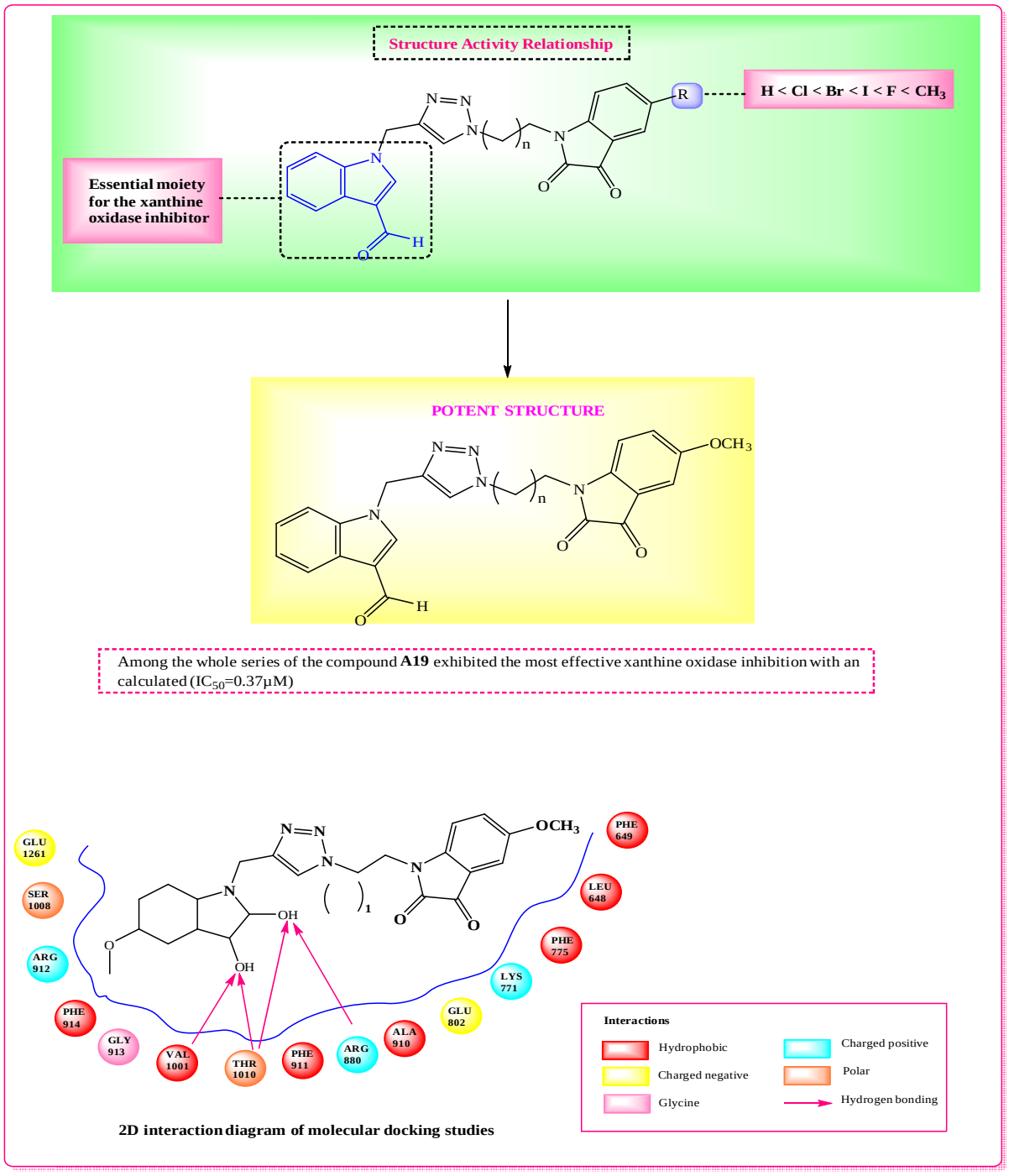


Figure 3: Represents the compound A19 will most effective xanthine oxidase inhibitors

Whereas designed and synthesized a SAR of C6-C3 phenylpropanoids to exhibited the promising xanthine oxidase inhibiting activity and Antioxidant activities that neutralize free radicals for the potent molecules. Using the methods of DNA relaxation, DPPH (1,1-diphenyl-2-picrylhydrazyl hydrate), and DMPO (5,5-dimethyl-1-pyrroline-N oxide)-electron spin resonance (ESR), the study examined the effects of 11 specific C6-C3 phenylpropanoid variants on the suppression of reactive oxygen species (ROS) under the oxidative conditions. Furthermore, the study also examined the effects of potent molecules of xanthine oxidase inhibitors and examined the structure activity relationships of these potent molecules against the activity of xanthine oxidase inhibitors.

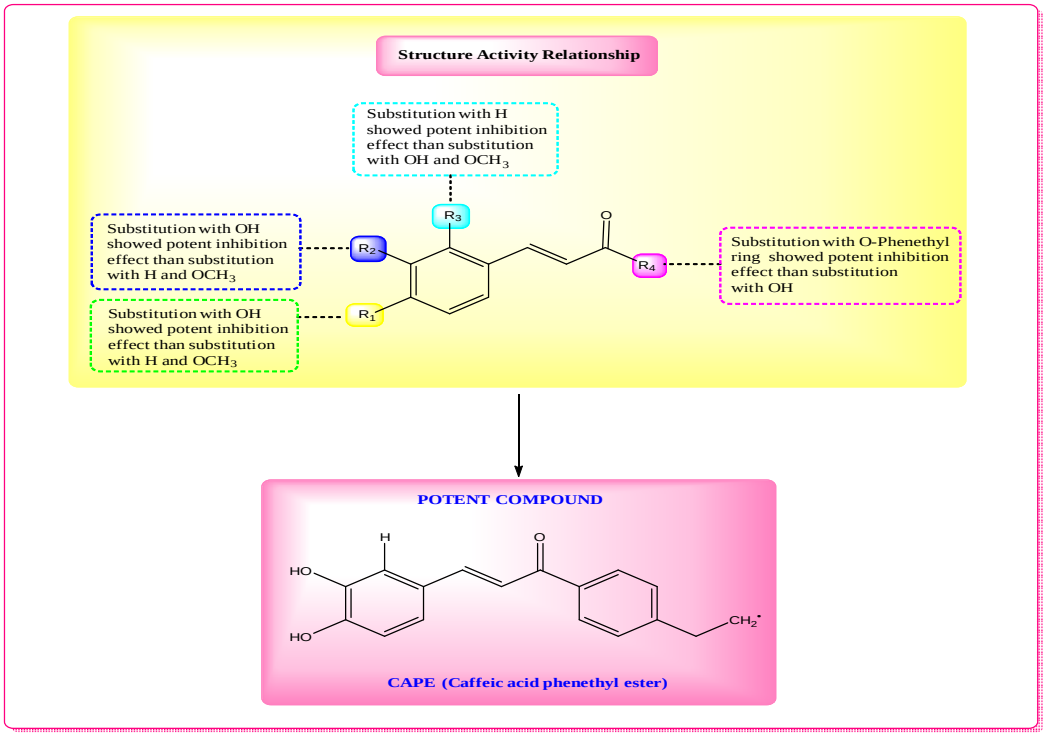


Figure 4: Represents the Novel Xanthine Oxidase Inhibitors (Caffeic acid phenethyl ester)

Computer aided molecular modelling technique were used to investigated the activity of xanthine oxidase and as well as also used for free radical-scavenging activities. Total 11 compounds were tested out of which CAPE (caffeic acid phenethyl ester) were showed the most potent inhibition against the xanthine oxidase activity and furthermore, CAPE were the potent compound for the protecting cells against the reactive oxidant species mediated which also showed the best inhibition activity against the reactive oxidant species. CAPE were exhibited best xanthine oxidase activity with calculated percentage inhibition **73.93 ± 3.24** of Scavenging effects on stable DPPH radicals by phenylpropanoid derivatives.

Subsequently, compound CAPE also exhibited the IC_{50} of **6.26 ± 1.60** against the xanthine oxidase by phenylpropanoid agents. CAPE had two hydroxyl groups on the benzene moiety in their chemical structures, and it was possessed a better in scavenging radicals than additional chosen substances, and it was also the strongest XO inhibitors (*Chang et al.*,2007).

Conclusion

In conclusion, this review highlights the therapeutic potential xanthine oxidase inhibitor which will minimize the effect of xanthine oxidase enzyme responsible for formation of free radicals. Which will further lead to the number of chronic disorders as discuss in the article. While significant progress has been made, further research is necessary to optimize its efficacy, minimize adverse effects, and explore novel formulations or combination therapies. deeper understanding of its pharmacokinetics, pharmacodynamics, and clinical applications will pave the way for its broader therapeutic use. Even though there has been a lot of progress, more study is required to maximize its effectiveness, reduce side effects, and investigate new formulations or combination treatments. Its wider therapeutic use will be made possible by a better understanding of its pharmacokinetics, pharmacodynamics, and clinical applications.

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