Review Paper:

Role of Tannase in Chronic Diseases: A review

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Abstract
Tannase is an inducible and extracellular microbial enzyme that hydrolyses the ester and depside linkages of tannic acid in hydrolysable tannins to release glucose, gallic acid, ellagic acid and propyl gallate. Tannase or tannin acyl hydrolase is an enzyme and has several applications in the field of science and technology. It is produced by different bacteria like lactobacillus, staphylococcus aureus, yeast and majorly by fungi. Due to its hydrolytic properties, tannase could be used to reduce the ill effects of tannins in beverages, food and tannery effluents for the production of gallic acid from tannin rich materials.

Tannase is a natural anti-oxidant phenol found in numerous fruits and vegetables and various plant parts. The anti-proliferative and anti-oxidant properties of Tannase have prompted research into its potential health benefits. Despite tannase is considered as an important industrial enzymes,the present review describes its role in various chronic diseases.

Keywords: Tannase, gallic acid, propyl gallate, ellagic acid.

Introduction
Tannin acyl group hydrolase or tannase is a cytomembrane sure catalyst, secreted into the living thing space, helps in breaking of organic compound bonds into tannins which can be hydrolysed like phenol and produces aldohexose and gallic acid which result in the production of propyl gallate and ellagic acid as shown in flow chart.[1,19,59] Chemical formula for industrial phenol is usually given as $C_{76}H_{52}O_{46}$ that represents decagalloyl aldohexose, however it is a combination of polygalloyl quinic acid esters or polygalloyl glucoses with the quantity of galloyl moieties.

After cellulose, hemicellulose and lignin polymer, tannins represent the fourth most overabundant plant constituent[59]. Tannis are poyphenolic compounds and located in virtually each part of the plant like seeds, fruit, root, wood, bark and leaf[95].

Tannase plays a very crucial role in different areas and some of them are food industries, chemical industries and pharmaceutical industries, additionally it plays very important role in the production of animal feed, production of beer and the treatment of effluent of tanneries[107,108] also for the assembly of acid, a substrate for radical gallate production, in trimethoprim synthesis[82,83] and as a substrate for production of alternative esters of acid. Preliminar studies of tannase concentration among microorganism origin have been done, then it is found that a most popular tannase producer is fungi as hostile, yeasts and bacteria; however, the reports on catalyst production by these organisms are restricted[4].

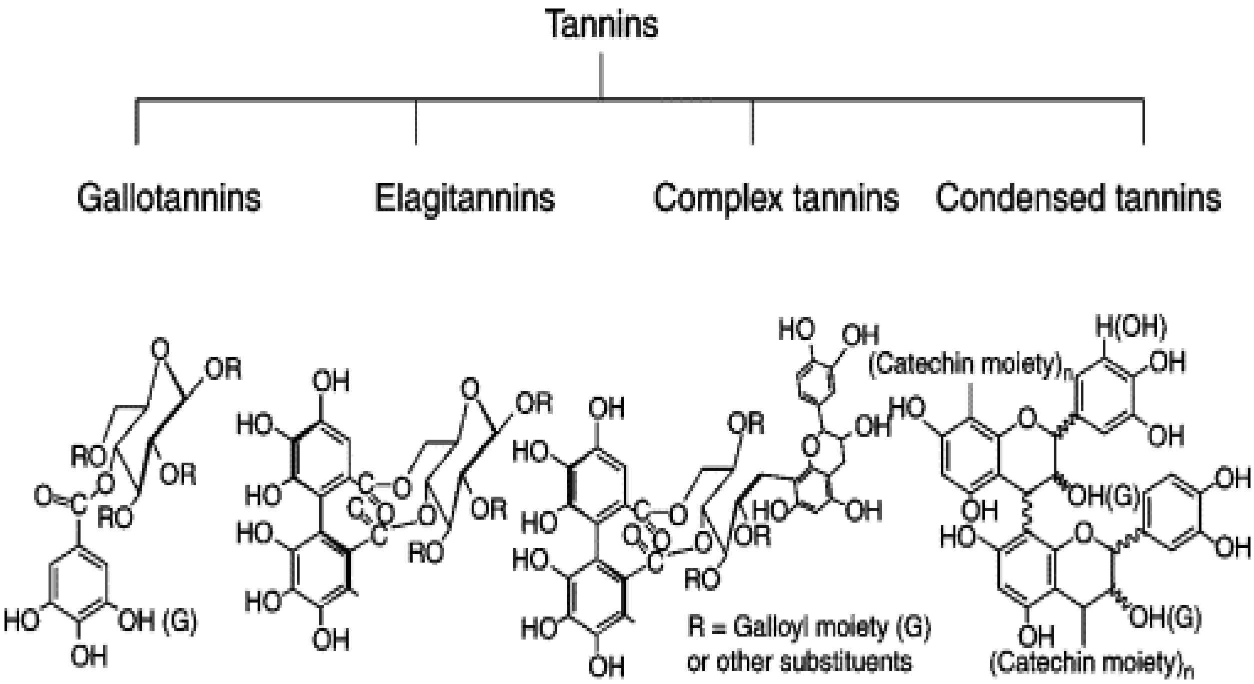

Fig. 1: Structure of tannins[23]

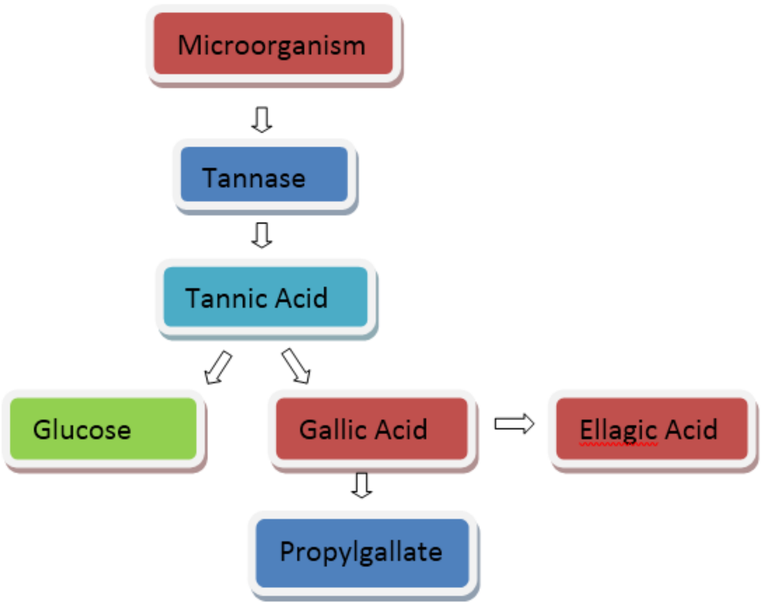

Fig. 1: Flow diagram of tannin degradation in gallic acid, ellagic acid and propyl gallate

Major tannase producers embody fungi like *Aspergillus* sp., *Penicilium* sp., *Fusarium* sp. and *Trichoderma* sp.

On the other hand, some forms of yeasts and microorganism are notable to supply tannase. These comprises, *Debraryomyces* sp., *Cyberlindnera* sp. and *Sporidiobolus* sp. as yeast varieties[57] whereas *Streptococci* sp., *Enterobacter* sp., *Cynobacteria* sp. and *Eubacterium* sp. as prominent bacterial producer.

Tannase which are produced by microorganisms, are strongly associated with a reduced risk for developing chronic diseases such as cancer and cardiovascular disease. In view of above the current review targeted the role of tannase in different human diseases.

Role of tannins in plants

"Tannin" expresses tanning substance which is present in the foremost thick reserve materials of plants. Tannins are gifts in each flowering and seed-producing plants, particularly in several dicotyledons. The deposition of tannins will go on in any style of part of plant; different components of the plant contain different amounts of tannic acid, for example in the roots tannin is especially found within the layer, underneath the cuticular layer where it protects the plant from pathogens. In the trunk it is gift within the active growth areas like secondary vascular tissue. Tannin is found in seeds, fruits and leaves, Tannic acid furnishes an astringent flavor that minimizes the craving of plant-eating insects and animals and therefore symbolizes a line of defense created by nature.

While returning to the importance of tannins in plants, Plants turn out tannins to safeguard themselves from intrusive on herbivores and microorganisms.[22] Tannins show biological properties like inhibitor activity, chelation of metal ions, precipitation of macromolecule etc.[42]

Tannins are also related to tartness and bitterness in fruits[1]. Different functions are associated with the vital role of tannins played within the seeds development and physiology, in the activation of the gens of nodulation that favor the regression of element within the plants and attraction of pollinating insects.[43]

Sources of tannase

Plant, animal and microorganism sources produce tannases, however, microorganisms are used for huge production of tannase in industries attributable to their diversity, consistency in the production of enzymes and comfort in downstream process. True fungal species including genus *Aspergillus* sp., genus *Penicillium* sp. and *Pichia* sp. are well-known tannase produces[53]. Genus *Aspergillus* sp. and genus *Penicillium* sp. are comparatively high yield producers of tannases and widely employed in major industries[39,76]. To date, commercially, tannases are chiefly made through the fungal fermentation, only crude enzymes are readily produced from the genus *Aspergillus* species[1].

Analysis over past 140 years resulted in the discovery of tannase producing microorganisms. 'Bacteria, fungi and yeasts' are the outstanding producers. Some animals even have also been found as the producer of tannase. The initial description of bacterial strains possessing tannase activity was reported by Deschamps et al.[32]

But in last twenty five years, more than few scores reports were printed on microorganism tannase and more than two scores of new tannase positive bacteria have been isolated which will utilize phenol because of the sole carbon supply[86]. Some species are given in table 1. Filiform fungi of the genus *Aspergillus* and genus *Penicillium* genus are wide employed for the production of tannase. A list of fungal tannase sources is given in table 2.

There are few reports of production of tannase through yeasts listed in table 3. Tannase has been reported to be gift in several tannin containg plant materials like fruits of *Terminalia chebula* (myrobolan), pods of *Caesalpinia coriaria* (divi-divi), leaves of *Angeissus latifolia* (dhawa) and also the bark of golden shower tree (konnam) and tree *Vachellia nilotica* (babul). Tannase from microorganisms is more stable as compared to plant tannase and purification is cumbersome[59].

Table 1
Bacterial Tannase sources

Microorganism genera
Achromobacter sp[39]
Bacillus[17]
Bacillus cereus[69]
Bacillus gottheilii M2S2[101]
Bacillus licheniformis[69]
Bacillus massiliensis[17]
Bacillus polymixa[15]
Bacillus sphaericus[82]
Citrobacter freundii[72]
Corynebacterium sp.[15]
Enterococcus faecalis[2]
Erwinia carotovora[92]
Klebsiella pneumoniae[15]
Klebsiella sp[81]
Lactobacillus. paraplantarum[104]
Lactobacillus. pentosus[104]
Lactobacillus. plantarum[85]
Lactobacillus[89]
Lactobacillus acidophilus[107]
Lactobacillus animalis[3]
Lactobacillus buchneri[41]
Lactobacillus hilgardii[41]
Lactobacillus murinus[3]
Lactobacillus paraplantarum[78]
Lactobacillus pentosus[78]
Lactobacillus pentosus[3]
Lactobacillus plantarum[78]
Lactobacillus sp. ASR-S1[91]
Microbacterium terregens[17]
Pantoea sp.[81]
Pediococcus acidilactici.[3]
Pediococcus pentosaceus[79]
Pesudomonas[96]
Providencia rettgeri.[17]
Pseudomonas aeruginosa[96]
Pseudomonas solanacearum[73]
Selenomonas ruminantium[15]
Serratia ficaria[17]
Serratia marcescens[17]
Serratia spp.[81]
Weisella confuse[41]

Table 2
Fungal Tannase sources

Microorganism genera
Aspergillus.nidulans[14]
Aspergillus. fumigates[66]
Aspergillus.Aculeatus
Aspergillus.Aureus[67]
Aspergillus.Awamori [23]
Aspergillus.Carneus[14]
Aspergillus.Fischerii[67]
Aspergillus.flavus[40]
Aspergillus.Fleviceps[67]
Aspergillus.japonicus[40]
Aspergillus.niger[6,7]
Aspergillus.oryzae[52]
Aspergillus.parasiticus[14]
Aspergillus.phoenicis[36]
Aspergillus.rugulosus[67]
Aspergillus.tamari[6]
Aspergillus.tereus[6]
Aspergillus.ustus[67]
Arxula adeninivorans[21]
Ascochyta biochemical[59]
Ascochyta boltshauseri[18]
Ascochyta Pisi[18]
Ascochyta viciae[67]
Aspergillus awamori MTCC 9299[25,26]
Aspergillus melleus[63]
Aspergillus niger[29]
Aspergillus oryzae[46]
Aspergillus tamarii [27]
Candida spp.[9]
Chetomium lobosum[67]
Cryphonectria parasitica [36]
Cryphonectria parasiticus [40]
Emericella nidulans [38]
Fusarium.oxysporium[67]
Fusarium.solani[40]
Fusarium subglutinans[44]
Helicostylum sp.[56]
Mucar pranii[18]
Neurospora sp.[72]
Penicillium. chrysogenum[1]
Penicillium. fellutanum[13]
Penicillium.carilophylum [67]
Penicillium.charlesii [83]
Penicillium.citrinium[13]
Penicillium.commune[13]
Penicillium.digitatum[13]
Penicillium.glabrum[12]
Penicillium.islandium[13]
Penicillium.notatum[40]
Penicillium.variable[98]
Paecilomyces variotii[65]
Penicillium acrellanum[1]
Rhizopus Oryzae[18]
Selenomonas ruminantium[100]
Trichoderma hamantum[13]

Table 3
Yeast Tannase sources

Microorganism genera
Arxula adeninivorans[13]
Aureobasidium pullulans DBS66[12]
Candida sp[9]
Candida utilis[99]
Debaromyces hansenii[31]
Mycotorula japonica[15]
Paradoxa. Monospora[9]
P. pseudopolymer.[9]
Pichia adzetti[13]
Pichia spp.[1]
Saccharomyces cerevisiae[110]

Applications of tannase in medical field

Tannase has a very keen role in numerous areas like food industries, chemical industries and pharmaceutical industries, additionally, within the production of animal feed, production of beer and the treatment of effluent of tanneries[107,108] also for the assembly of acid, a substrate for radical gallate production, in trimethoprim synthesis[82,83] and as a substrate for production of alternative esters of acid. Besides the industrial uses, tannic acid is recently being used in the treatment of chronic diseases which is the interesting aspect of study.

Gallic Acid Production: One of the major applications of the enzyme is in gallic acid production. Gallic acid (3,4,5 trihydroxybenzoic acid, GA) is an organic compound with chemical formula $C_6H_2(OH)_3COOH$. Gallic acid is colorless in its pure form and exists in crystalline form with melting point 250 ^oC and molar mass 17.12 g/mol[37]. Gallic acid has wide range of applications in different industries from health and food to dyes, inks, paints and photography[101]. Gallic acid is employed in the production of an antiprotozoal/antimalarial drug Trimethoprim which could be a substrate for the chemical and catalyst synthesis of group gallate (antioxidants in fats and oils) and in beverages industries[58].

Anti-Aging and weight loss Treatment: The loss of skeletal muscle associated with aging causes functional disability due to the loss of strength, risk of falls, fracture and loss of autonomy[50]. The number of patients with sarcopenia is expected to rise as the aging population continues to increase globally. Green tea harvested from *Camellia sinensis* contains polyphenols and it is widely used in nutraceutical and pharmaceutical industries. Hong et al[49,50] recently explained the effects of tannase-converted green tea extract on skeletal muscle development for the treatment of aging problems. One more research related to aging effect was done by Homg et al[49,50] on mice by photoprotective effects of a formulation containing tannase-converted green tea extract against UVB-induced oxidative stress in hairless mice.

Furthermore, tannase and pectinase treatments induced the biotransformation of catechins and altered the tea polysaccharide (TPS) content. Also, hydrolysis on polysaccharides by pectinase significantly increased TPS-induced Interleukin 6 (IL-6) production in macrophages. In particular, treatments of rapidase (TPS-Ra) led to the highest IL-6 production among TPS samples, similar to treatment of highly-purified pectinase (TPS-GTE)[11]. It also has been tried that the conventional tea comparatively shows lower inhinbitor property but tannase treated tea shows higher inhibitor properties than the conventional tea. Chen in Xu et al[24] in their study supported the possibility that green tea has preventive effects against liver cancer as green tea has also been proved to have lipid-lowering activity which makes it effective for weight loss.

Skin diseases: *Atopic dermatitis* (AD) is a chronic inflammatory skin disease that causes severe itching and dry skin after contact with aeroallergens such as house dust mites, pollen and animals. Some drugs like anti-histamines, steroids and immunosuppressive agents have been used for the treatment of AD but long-term use of these drugs causes many side effects also. To overcome these side-effects, green tea extract treated with tannase is an effective treatment for AD[51].

Cancer Treatment: It is utilized for the treatment of allergic diseases such as allergic rhinitis, asthma, sinusitis by inhibiting histamine discharge and expression of pro inflammatory cytokine and its antimicrobial action is also reported against human and plant pathogens. Phenolic acids such as caffeic acid (CA) (3, 4-dihydroxycinnamic acid) and gallic acid mechanisms suggested for their anticancer effects include stimulation of *P53* and *P21* gene expression and inhibition of CDK2 gene expression which may lead to G0/G1 arrest in the cell cycle to cure breast cancer. Also gallic acid has been found to induce apoptosis of cancer cells without harming normal cells by the mitochondria-driven pathways and to show selective toxicity for cancer cells. Seresht in et al[97] focused on the intrinsic apoptotic signaling pathway, as a major apoptosis pathway and the relationship between these genes and gallic acid.

For the treatment of cancer, nanodrugs are also being invented. The selection of gallic acid as a model drug to be loaded onto the nanocarrier formed a new nanocomposite like graffine oxide and gallic acid for active drug delivery and specific cell targeting system in normal fibroblasts (3T3) and in liver cancer cells, HepG2[33]. Also gallic Acid enhanced the gold nanoparticle in anticancer activity in cervical cancer cells in both HPV-positive and HPV-negative cervical carcinoma cells[28]. There are multiple mechanism of gallic acid which can resist tumor development such as the metastasis inhibition;[77] angiogenesis suppression[63]; apoptosis induction and/or necrosis[109]; cell viability, proliferation, invasion and tube formation inhibition[64]; and migration and invasion inhibition[60].

You et al[109] reported that gallic acid-induced apoptosis in HeLa cells was attended by the slight down-regulation of Bcl-2 and the up-regulation of Bax indicating that the mitochondrial release of cytochrome c can be controlled by the Bcl-2 family of proteins. Besides human breast cancer and liver cancer, gallic acid and propyl gallate also aid to cure colon cancer[102], ovarian cancer[47] and prostate cancer[48,54,93].

Kidney Failure: Renal ischemia-reperfusion injury (RIR) is caused due to sudden temporary loss of the blood flow to the particular organ. RIR usually is related to a robust inflammatory and oxidative stress response to hypoxia and reperfusion which alter the organ function. The protective function of GA is due to its ability to inhibit ROS induced cellular damage, induce apoptosis of cancerous cells, up-regulate glutathione peroxidase (GPX) expression and mitigate the presence of free radicals and it is found in the pre-treatment of GA on kidney function and oxidative stress in an *in vivo* rat model of RIR treatment[5].

Treatment of Tumors: Ellagic acid is hydrolysable tannin present in the majority of the plants and synthesized catalytically from ellagitannins. Ellagic acid reacts in the human body that may upgrade good health and is effective in the cure of cancer, heart diseases and other chronic diseases. Nowadays, the demand for natural ellagic acid is increasing due to its use in the food industries as well as in pharmaceutical industries. Ellagitannins and ellagic acid communicate with the cell walls or sites to ease to build-up complex protein, which prevents the formation of tumors by inhibiting and proliferation of metastatic cells[111]. Derosa et al[30] explained the role of ellagic acid in chronic diseases.

Treatment of Malignant Cancer: Hepatocellular carcinoma (HCC) is the malignant cancer deduced from hepatocytes and is the most common cancer worldwide. Propyl gallate, propyl-3,4,5-trihydroxybenzoate, a polyphenolic compound family is synthesized by the condensation of gallic acid and propanol. Propyl gallate shows protective effects against oxidation by hydrogen peroxide and oxygen free radicals via a catalytic effect.

A study by Wei in et al[106] shows propyl gallate with various anticancer effects as a therapeutic choice for HCC. As stated earlier, PG treatment induces growth inhibition of HCC cells both *in vitro* and *in vivo*. PG-induced HCC cells death through the mitochondria-related apoptosis involves Bcl-2, Bax, Bad, caspase and cleaved Poly (ADP-ribose) polymerase (PARP).

Other Applications: Applications of tannase in food and potable industrial product leads to get rid of tannin's undesirable effects. Enzymatic processing of fruit juices to scale back the bitterness, possesses benefits to enhance the quality of juices by depressed haziness and non-adulteration of the quality of juices. New types of fruit juices have been produced for health advantages recently, for inhibitor potential ability of disease-fighting. High tannic acid amount in the fruits is chargeable for daze and formation of sediment, further as for physical appearance, bitter taste and stypsis nature of the juice when to store.

Tannase is additionally used as instructive medium in wines, juices of fruits and energizing drinks with low flavors. Just in the matter of wines, the tannins are usually oxidised by the contact of air into quinones which result in unsuitable murkiness leading to a heavy caliber drawback. The use of tannase offers a meaningful answer for the same. Within the production of brewage, one of the form of tannins is added known as hops. Higher quantity of proteins within the brewages leads to an unsuitable mukiness. This is often beacuase of complicated formation between super molecule and also the hops tannic acid. The use of tannase may well resolve this drawback[15].

Recombinant tannase: Currently, a dozen or more bacterial proteins possessing tannase activity have been recombinantly produced and biochemically characterized. Among these, we find proteins from a diverse range of bacterial species, from the phyla Firmicutes *(Lactobacillus plantarum* and *Streptococcus gallolyticus* strains, among others), Actinobacteria *(Atopobium parvulum, Streptomyces sviceus*) and Fusobacteria *(Fusobacterium nucleatum*). Need for the recombinant tannases is due to different types of tannases that can work at a wide range of physical parameters such as temperature, pH, ionic strength and presence of detergents and organic solvents need to be identified for better production of tannase[86].

Conclusion

Tannase seems to be a very promising agent for the treatment of chronic diseases, especially cancer as it seems to have anti-cancer properties. It is also important enzyme involved in many industrial processes. Recombinant tannase production and different immobilization techniques need to be studied in detail for further research in this area of medical field.

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