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Biochemical and Biophysical Research Communications 734 (2024) 150774

Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

Glutathione S-transferase: A versatile and dynamic enzyme

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ARTICLE INFO

Keywords:
Glutathione S-Transferase
S-Glutathionylation
GST polymorphism
Oxidative stress
Biotransformation
Cellular detoxification

ABSTRACT

The dynamic and versatile group of enzymes referred to as glutathione S-transferases (GSTs) play diverse roles in cellular detoxification, safeguarding hosts from oxidative damage, and performing various other functions. This review explores different classes of GST, existence of polymorphisms in GST, functions of GST and utilizations of GST inhibitors in treatment of human diseases. The study indicates that the cytosolic GSTs, mitochondrial GSTs, microsomal GSTs, and bacterial proteins that provide resistance to Fosfomycin are the major classes. Given a GST, variation in its expression and function among individuals is due to the presence of polymorphic alleles that encode it. Genetic polymorphism might result in the modification of GST activity, thereby increasing individuals' vulnerability to harmful chemical compounds. GSTs have been demonstrated to play a regulatory function in cellular signalling pathways through kinases, S-Glutathionylation, and in detoxification processes. Various applications of bacterial GSTs and their potential roles in plants were examined. Targeting GSTs, especially GSTP1-1, is considered a potential therapeutic strategy for treating cancer and diseases linked to abnormal cell proliferation. Their role in cancer cell growth, differentiation, and resistance to anticancer agents makes them promising targets for drug development, offering prospects for the future.

1. Introduction

The Glutathione S-transferases (GSTs) are crucial Phase II biotransformation enzymes that play significant role in cellular detoxification, serving as a safeguard against damage from electrophilic species, cancer-causing environmental substances, reactive oxygen species (ROS), and chemotherapeutic medications [1]. They have a broad distribution across different organisms and are seen in both prokaryotic and eukaryotic systems as the primary Phase II enzymes responsible for biotransformation [2]. They form a superfamily of widely present and versatile enzymes, referred to as GSTs (EC 2.5.1.18), that facilitate the nucleophilic coupling of the tripeptide glutathione (GSH; g-Glu-Cys-Gly) to various harmful foreign compounds, such as electrophilic compounds and cancer-causing metabolic byproducts produced during phase I metabolism [3]. This process neutralizes their electrophilic properties, making the culminating compounds more hydrophilic and aiding their removal from the cell through Phase III enzymes [4].

Furthermore, GSTs have the capacity to function as isomerases, peroxidases, and thiol transferases [5]. Moreover, they have the potential to participate in non-enzymatic roles, such as influencing signalling pathways and binding to ligands that are not substrates [6]. Besides, GSTs play crucial functions in signal transduction and various cellular activities. For example, GSTP is known to regulate c-Jun N-terminal kinase (JNK) signalling [7], and GSTM from mice can form suppressive complexes with Apoptosis Signal-regulating Kinase 1 (ASK1), a member of the Mitogen-Activated Protein (MAP) kinase pathway [8]. Additionally, members belonging to Alpha and Sigma classes are implicated in sex steroids and prostaglandins biosynthesis [9,10]. The absence or mutations in specific GSTs are linked to several human disorders such as Parkinson's, Alzheimer's, and an increased risk of cardiovascular diseases [11,12]. Furthermore, GSTs are believed to contribute to resistance against certain chemotherapeutic and carcinogenic compounds [13].

GSTs are categorized according to their protein sequences and structures. The elucidation of the first GST structure in 1991 marked the beginning of a surge in the availability of structural information for GSTs from the three major groups including cytosolic GSTs, mitochondrial GSTs, and the membrane-associated proteins engaged in the metabolism of eicosanoid and glutathione, collectively referred to as the Membrane Associated Proteins in Eicosanoid and Glutathione metabolism

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https://doi.org/10.1016/j.bbrc.2024.150774
Received 20 July 2024; Received in revised form 19 September 2024; Accepted 30 September 2024
Available online 1 October 2024
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(MAPEG) family [14].Within the cytosolic GST family, those in the same class display over 40 % similarity in their amino acid sequences, while proteins from distinct classes show less than 25 % sequence identity [14]. In the human body, cytoplasmic GST isoforms belonging to classes including Theta, Alpha, Mu, Zeta, Pi, Sigma, and Omega can be found. The GSTs belonging to the mitochondrial class have a profound evolutionary connection with those of cytosolic class and are categorized as class Kappa. Notably, each of cytosolic GSTs and mitochondrial GSTs tend to form dimers, and there have been instances where heterodimers of cytosolic GSTs were discovered, involving chains from identical class.

In this review, various categories of GST, the biochemistry underlying GSTs, the presence of polymorphisms in GST, the roles of GST, and the applications of GST inhibitors in the treatment of human diseases were explored.

2. The mechanism of GST catalytic action

The core mechanism driving all GST catalytic actions revolves around the enzymes' capability to reduce the sulfhydryl group's pKa within reduced glutathione (GSH) from 9.0 in an aqueous environment to approximately 6.5 when GSH becomes conjugated in the enzyme's active site [15]. When GSH is associated with GST, it adopts the thiolate (GS^-) anionic state at a neutral pH. The catalytic process mediated by GST hinges on the enzyme's dual function of encouraging GS^- production and effectively binding hydrophobic electrophilic compounds in a closely adjoining location [13]. The regions responsible for binding of GSH and the hydrophobic substrates have been respectively denoted as the G-site and H-site [16]. With specific substrates including phenethyl isothiocyanates and benzyl, as well as alkyl dihalides, GST has the capacity to facilitate both the forward and reverse reactions. This can result in heightened toxicity rather than detoxification [13]. In its active cytosolic state, the enzyme is structured as a dimer consisting of two subunits [13,17].

Studies using X-ray crystallography have demonstrated that a conserved tyrosine (in Alpha, Mu, Pi, and Sigma classes) or serine (in the Theta class) located at the N-terminus of most cytosolic GSTs is engaged in hydrogen bonding to stabilize GS [18–21]. The suggestion is that immediately GS^- is generated within the active domain of GST, it gains the ability to undergo a spontaneous reaction, involving nucleophilic attack, with electrophilic xenobiotics located in a short distance [22]. Hence, the catalytic action of GST is as a result of the enzyme's combined ability to encourage the creation of GS^- and to bind hydrophobic electrophilic compounds in a closely adjoining region. The site for binding of glutathione displays a high level of specificity [23], whereas, conversely, the second substrate-binding site showcases a broad specificity for hydrophobic substances.

3. GST classes

GSTs found in eukaryotes and aerobic prokaryotes are categorized into four significant families of proteins including mitochondrial GSTs, cytosolic GSTs, microsomal GSTs, and bacterial proteins that offer resistance to Fosfomycin [2,24–26]. However, human GSTs are classified into cytosolic, mitochondrial, and microsomal forms [27]. Seven classes of human cytosolic GSTs including Alpha, Mu, Pi, Sigma, Omega, Theta, and Zeta have been identified based on their similarities in sequence, specificity towards substrate, and immune responses. Microsomal GSTs are also known as membrane-associated proteins in eicosanoid and glutathione metabolism (MAPEGs) [28]. In mammals, mitochondrial GSTs, identified as the Kappa class, are primarily situated in the mitochondrial matrix [29] and peroxisomes [30]. Studies have revealed that human mitochondrial GSTs play crucial functions in biotransformation of lipid peroxide and metabolism of lipid [30]. Microsomal GSTs are part of the MAPEG family, actively contributing to the decrease of lipid peroxidation and the detoxification of xenobiotics [31,32]. Cytosolic GSTs differ from mitochondrial and microsomal GSTs in that they reside in the cytoplasm and are present in a soluble state [33].

The MAPEG group is subdivided into four labelled as I to IV. There is less than a 20 % sequence similarity among protein sequences in different subgroups. In the human population, six MAPEG isozymes have been detected, distributed in subgroups I, II, and IV [34]. Similar to cytosolic and mitochondrial GSTs, numerous MAPEGs, including microsomal GST1 (MGST1), facilitate the binding of GSH to various electrophilic substances. Additionally, some other MAPEG members are implicated in enzymatic functions related to leukotriene and prostaglandin production [2].

Although GSTs have traditionally been categorized into various family-like classes, an additional hierarchical classification is needed to clearly outline the relationships among the major subgroups. Despite the similar structure of all cytosolic GSTs, a structure similarity network reveals that the Alpha, Mu, Pi, and Sigma classes of the Y-type major subgroup, primarily found in eukaryotes, are considerably more alike to each other compared to the classes in the other main GST subclass [35]. Although these groups have significant distinguishing features, like the additional active site helix in the Alpha class [21] and the hydrophilic dimer interface in the Sigma class [36], they are closely grouped together when considered within the broader GST superfamily. Similar eukaryotic classes are referred to as tyrosine-type GSTs (Y-GSTs) due to their mechanism involving tyrosine and glutathione interaction. The other primary subclass of cytosolic GSTs are called serine/cysteine type GSTs (S/C-GSTs) [35].

The most significant distinction between the two groups is the presence of a tyrosine at the terminus of the first beta strand (B1) in Y-GSTs, compared to a serine or cysteine at the onset of helix 1 (H1) in the second major subgroup. These amino acids are conserved and are essential for catalytic activity in most identified enzymes. The tyrosine hydroxyl group in Y-GSTs is considered to donate a hydrogen bond to the sulfur atom of GSH, which reduces its pKa and stabilizes a nucleophilic thiolate [37]. Members of S/C-GSTs typically use the amino acids in their active site in a similar way, with some differences. The activation of GSH in Theta class GSTs is facilitated by the hydroxyl group of serine, a role that serine also plays in the Phi and Tau classes [38,39]. However, within the Omega class, a cysteine in the active site interacts with glutathione to form a disulfide bond, displaying "thioltransferase" activity linked with glutaredoxins, and is undetectable by traditional biochemical GST assays [5]. Essential for their function, Zeta class enzymes have a crucial serine and a reactive cysteine at the active site for binding GSH, though this cysteine is not essential for catalytic activity [40,41]. The Beta class, another distinct S/C-GST group, binds GSH through a mixed disulfide bond to a conserved cysteine [35].

Omega-class isozymes, akin to all cytosolic GSTs, exhibit an N-terminal domain similar to thioredoxin and a specific helical C-terminal domain [14,42]. In contrast to most GSTs, where active sites typically include a serine or tyrosine hydroxyl group that aids in ionizing the GSH sulfhydryl group, Omega-class isozymes such as hGSTO1 and hGSTO2 possess a cysteine residue (C32) in their active sites. This cysteine residue undergoes oxidation via the generation of an enzyme-GSH mixed disulfide, accompanied by a co-substrate reduction. Hence, the Omega-class isozymes serve as thiol transferases or reductases, facilitating processes like the reduction of dehydroascorbate and monomethylarsenate [42]. In mammals, MAPEGs employ a GSH-dependent isomerase activity to participate in the production of leukotrienes (such as FLAP and LTC4 synthase) or prostaglandin E (PGES) [43].

Across animals, plants, bacteria and fungi, about 36 classes of GSTs have been identified. A more precise classification was suggested through phylogenetic analysis of photosynthetic organisms. Employing phylogenetic investigation, eukaryotic organisms with photosynthetic capacity can be categorized into fourteen classes. Notably, the Phi, Zeta, Tau, Theta, and TCHQ classes feature GSTs having serine as the active site amino acid, while the catalytic residue nature in the EF1Bγ and Ure2p classes remains uncertain. The remaining 7 classes, including

Hemerythrin (GSTHs), DHARs, Iota (GSTIs), Lambda (GSTLs), GHRs, mPGES-2 s, and metaxins, are classified as Cys-GSTs [44,45] due to the presence of members exhibiting a highly preserved cysteine in the binding domain.

4. Polymorphism in GST

Gene polymorphism denotes the presence of multiple genetically influenced phenotypes within a given population. This involves variations in specific DNA sequences, such as single nucleotide polymorphisms (SNPs), recombination, sequence repeats, and addition or deletions [46,47]. The occurrence of polymorphism can be attributed to either random chance processes or external agents that induce it [48]. Genetic mutations causing polymorphism involve lasting modifications in the polymeric chain of a gene, creating a chain/sequence that varies from the greater number of subjects [49]. Genetic polymorphism in enzymes responsible for metabolizing drugs lead to the emergence of distinct subgroups within the population, resulting in differences in biotransformation of drug. This polymorphism within the genes of these enzymes can either provoke or eliminate their activeness [50]. It is a widespread phenomenon observed in several enzymes responsible for drug and xenobiotic metabolism [51]. By utilizing predictive genotyping of genes (i.e. identifying genetic variations or mutations that are associated with diseases or conditions) related to drug metabolism, it is possible to create secure, personalized, and cost-effective drug treatments [51]. For instance, busulfan plays a vital role in high-dose chemotherapy for bone marrow transplants, with its metabolism being heavily impacted by genetic variations in the GSTM1 gene. Individualizing busulfan doses through GSTM1 genotyping is vital in high-dose chemotherapy for bone marrow transplants. This strategy takes genetic variations in metabolism into account, helping to minimize side effects like veno-occlusive disease and achieve optimal drug efficacy [52–54]. Genotyping for GSTM1, as well as other GST genes such as GSTA1 and GSTT1, offers important insights that can aid in refining busulfan dosing strategies [52,54]. Tailoring dosages according to GST genotypes can lower the risk of complications like hepatic veno-occlusive disease (HVOD) and enhance overall treatment success [52,54].

Studies on the genetics of common complex diseases have concentrated on finding risk genes to develop new therapies and enhance diagnosis. This method has uncovered a number of significant genes [11]. Variations in GST genes have been identified as risk factors for various types of cancer [55]. Polymorphisms within numerous GST genes can alter the transcription or functional activity of the proteins they encode [28]. Most human GSTs contain genetic variations, mainly single nucleotide polymorphisms (SNPs) and occasionally deletions.

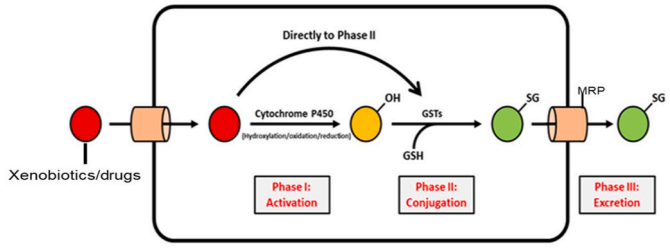


Fig. 1. Illustration of the biotransformation pathway of xenobiotics. Upon entering the cell, harmful molecules undergo processing by various enzymes within the detoxification system. Phase I enzymes, such as Cytochrome P450s, metabolize lipophilic molecules. The activated xenobiotics then undergo conjugation with GSH by phase II biotransformation enzymes, GSTs. In the final phase (Phase III), *trans*-membrane multidrug resistance-associated proteins (MRPs) from the C family of ABC transporters facilitate the export of these conjugated compounds out of the cell. Additionally, certain compounds with a polar or hydrophilic nature may directly enter Phase II metabolism.

Understanding how these variations impact clinical outcomes in cancer treatment is currently a significant area of research, with particular attention on GST classes Alpha, Mu, Pi, and Theta [28].

GSTs are inherently polymorphic, with enzyme levels depending on both induction and genetic polymorphism [56]. Genetic diversity in xenobiotic-metabolizing enzymes leads to variations in the metabolism of pro-carcinogens and carcinogens, influencing individual susceptibility to cancer. Consequently, genetic polymorphisms are potential risk modifiers. The GST family is characterized by abundant polymorphisms, especially in the GSTM1, GSTT1, and GSTP1 classes, which have well-documented polymorphisms [57]. GSTM1 is key in removing numerous carcinogens, ROSs, and many chemotherapy agents, while GSTT1 is crucial in eliminating carcinogens found in the environment like as 1,3-butadiene and ethylene oxide present in smoke [58].

In individuals with the GSTM1 null (0/0) polymorphism, the gene encoding this isoform is entirely absent, leading to the absence of its enzymatic activity [59]. Numerous studies examining genetic susceptibility to air contamination and its effects on cardiovascular outcomes indicate that GSTP1 and GSTM1 are involved in the regulation of ROS) [60]. Additional studies have discovered a connection between the GSTM1 0/0 polymorphism and the incidence of heart failure [61,62]. Elevated intracellular and vascular cell adhesion molecule levels, linked to exposure to black carbon and particulate matter, are implicated in promoting atherosclerosis. The presence of the GSTM1 polymorphism plays a role in this interaction [63]. The presence of GSTP1 and GSTM1 polymorphisms has been linked with increased levels of the oxidative DNA damage marker 8-hydroxy-2′-deoxyguanosine and an increased risk of coronary artery disease (CAD) related to smoking [64–66].

GSTO1 gene polymorphisms have been correlated with a higher likelihood of developing human cancers such as hepatocellular carcinoma, cholangiocarcinoma, and breast cancer [67], while ovarian cancer has been linked to variations in the *GSTO2* gene [68]. According to the meta-analysis by Yu et al. [69], there is a heightened risk of bladder cancer linked to the GSTM1 null, GSTT1 null, and GSTM1/GSTT1 double-null genotypes. GSTP1, the primary GST isoenzyme, is predominantly present in the lungs and demonstrates increased expression in cancerous tissues compared to non-cancerous tissues [70]. Previous researchers, through their meta-analysis, demonstrated that the relationship between GSTM1 null polymorphism and cataract risk was either non-existent or had limited evidence. In contrast, the GSTT1 null polymorphism was notably associated with an increased risk of posterior subcapsular cataracts [71].

The alpha (α) GST genes exist in five forms known as GSTA1, GSTA2, GSTA3, GSTA4, and GSTA5, situated on chromosome 6 of human [72]. Under polymorphic conditions, variations in the base of GSTA1 alleles result in low expression and altered biotransformation, particularly in subjects undergoing hematopoietic stem cell transplantation, including bone marrow transplantation [73]. GSTA2 may play a role in heme and bilirubin transport. Additionally, GSTA3, identified as an uncommon subclass of alpha (α) GST by Morel et al. [30], is primarily involved in steroid biosynthesis and double-bond isomerization [9].

5. Functions of GSTs

The GSTs constitute a family that facilitates various glutathione-dependent reactions. Apart from their role in catalysing conjugate formation, GSTs could equally function as peroxidases and isomerases [74]. They are vital for the daily detoxification process in body cells, protecting them from harmful substances [75]. The effectiveness of this detoxification activity is closely tied to each person's capacity, which is influenced by their genetic makeup [76,77]. Besides their vital role as detoxification enzymes, GSTs are involved in critical roles such as cell signalling, post-translational modifications, and resistance to anticancer drugs [78]. For instance, the Pi and Mu classes of GSTs influence the MAPK signalling pathway, which governs response to stress, cellular proliferation, and apoptosis, by directly interacting with JNK1 and ASK1

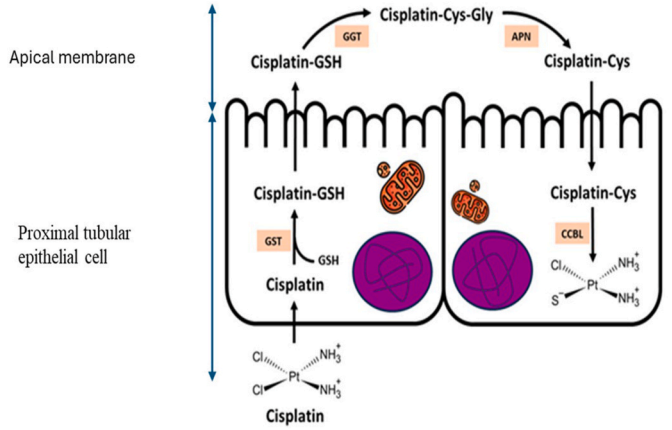


Fig. 2. Cisplatin bioactivation into a nephrotoxin involves a series of steps. Initially, Cisplatin undergoes conjugation with GSH facilitated by GST. The resulting Cisplatin–GSH conjugate is transported into the tubule lumen through MRP2 efflux, where it undergoes cleavage by γ-glutamyl transpeptidase (GGT) to form a cysteinyl–glycine conjugate. Subsequent cleavage by aminopeptidase (APN) yields Cisplatin–Cysteine. The Cisplatin–Cys conjugate is then reabsorbed by the proximal tubule, where it undergoes further metabolism by a pyridoxal 5′-phosphate-dependent enzyme known as cysteine S-conjugate beta lyase (CCBL) to produce a reactive thiol that can attach to proteins, potentially leading to toxicity.

[78,79]. They are also involved in processes like the synthesis of steroids and leukotrienes, the degradation of peroxides, *cis*-trans isomerization of double bonds, reduction of dehydroascorbate, Michael addition reactions, and noncatalytic ligandin activities, such as ligand binding and transport [14]. Additionally, GSTs are recognized for their role in enabling protein S-glutathionylation reactions, with several proteins, including PDI, p53, and Prdx-VI, identified as common substrates for GST-mediated protein S-glutathionylation [7]. Some of these roles/-functions performed by GSTs are reviewed below.

5.1. Detoxification function of GSTs

Cellular protection is achieved through the enzymatic activity of GSTs, which engage in the coupling of GSH with a diverse of hydrophobic and electrophilic compounds, such as carcinogenic substances, healing medications, and oxidative strain-related substances. This enzymatic process reduces the toxicity of these compounds and aids in their efficient elimination from the cell. Fig. 1 [2,80] provides an overview of xenobiotic detoxification for reference purposes.

It is widely acknowledged that the coupling of GSH with xenobiotics usually culminates in the production of passive metabolic products that can be excreted more effectively. Nevertheless, there are exceptions, such as GSH conjugates proving to be more reactive than their parent compounds in certain situations. This is exemplified in instances involving alkyl halides of short chain with dual functional groups. In particular, the interaction of GSH with dichloromethane gives rise to extremely volatile s-chloromethylglutathione adducts, which contain an electrophilic center capable of altering DNA [81,82], subsequently causing harmful effect. Additionally, the widely employed anticancer drug cisplatin is known to induce nephrotoxicity [83]. This takes place when GSH-linked platinum conjugates undergo metabolism within the kidney at the cells of the proximal tubule [84,85]. It was later demonstrated that this process takes place in a GSTP-controlled manner, employing both genetic and pharmacological repression *in vivo* [86,87]. The nephrotoxicity caused by cisplatin could be reduced by employing GSH mimetics [88][Fig. 2].

GSTs participate in the synthesis of mercapturic acid (Fig. 3) [89], specifically catalysing the initial step of a four-stage biosynthesis process. Subsequently, there is a stepwise detachment of the γ-glutamyl moiety and glycine from the glutathione conjugate, followed by the N-acetylation of the culminating conjugate of cysteine. These GSTs are integral components of a comprehensive safe-guarding strategy, and their efficacy relies on coordinated actions, such as the glutamate cysteine ligase and glutathione synthase provision of GSH. Additionally, they have the option to influence transporters facilitating the elimination of glutathione conjugates from the cell. Subsequently, the *trans*--membrane MRP expel these conjugates from the cell [2]. GST isoenzymes have demonstrated the ability to neutralize a diverse array of external substances, including carcinogenic substances, pharmaceuticals, and environmental pollutants.

5.2. GSTs and their impact on the regulation of cell signalling via kinases

The decline in the detoxification process of potential carcinogens, attributed to the absence or reduced GSTP expression, might contribute to the development of cancerous transformations and the advancement of diseases. Additionally, an upsurge in GSTP expression is closely linked

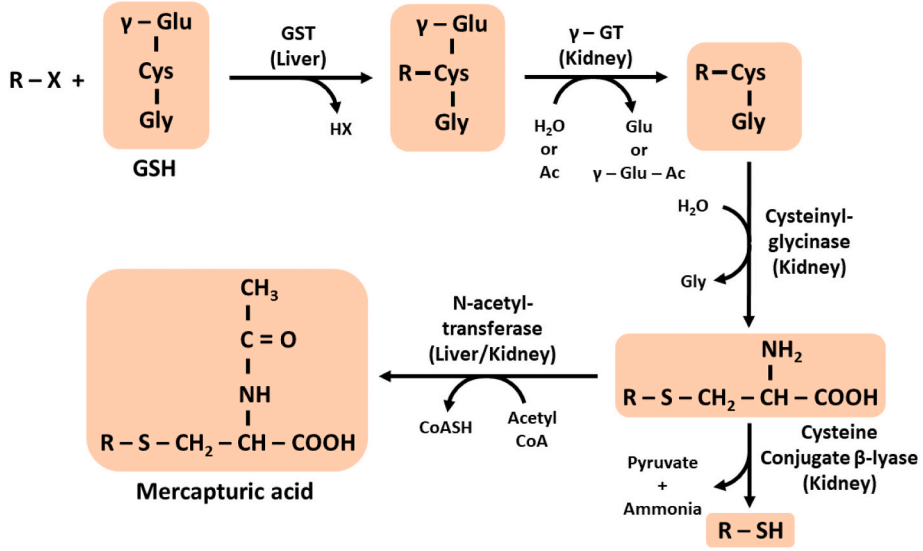


Fig. 3. Mercuric acid pathway of glutathione conjugates. The reaction catalyzed by cysteine β-lyase is also included. R-X, xenobiotics; GSH, glutathione; GST, glutathione transferase; γ-GT, γ-glutamyltransferase; Ac, γ-glutamyl acceptor.

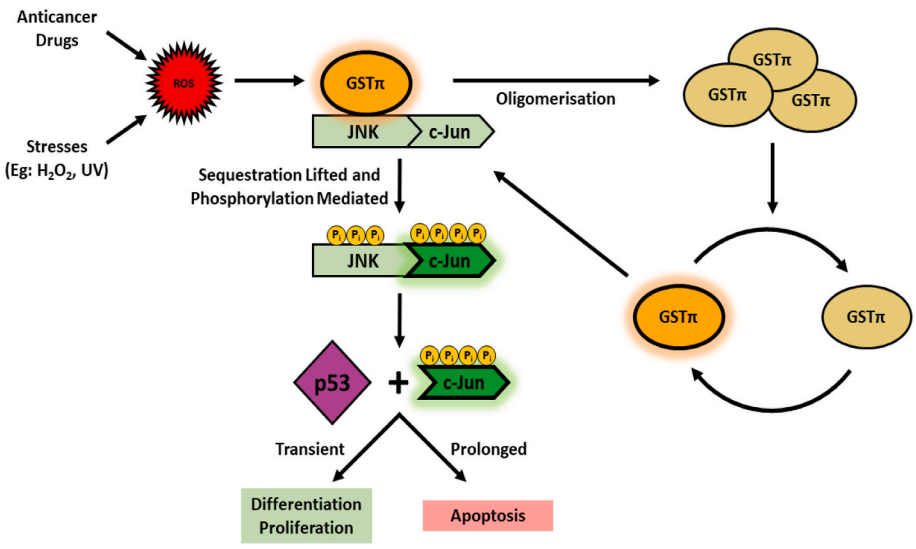


Fig. 4. Regulatory involvement of GSTS in the control of cellular signalling pathways via kinases, specifically highlighting the GSTP-Mediated activation of JNK

to multidrug resistance, owing to the limited affinity of GST-mediated GSH coupling for most of chemotherapeutic drugs. Hence, the control exerted by GSTs on kinase-dependent proliferation pathways is of higher importance than their simple catalytic functions [90].

GSTs engage in interactions among proteins with essential kinases while overseeing cellular transduction that governs proliferation, stress response and apoptosis. Through the sequestration of signalling kinases, they exert a negative influence on various signalling pathways. Specifically, GSTP is identified as an inhibitor of Jun kinase (JNK), and GSTM1 adheres to and hampers the action of ASK1 [8,91]. JNK is associated with signalling pathways that promote apoptosis, and ASK1 functions as MAP kinase. The process entails the stimulation of JNK through the

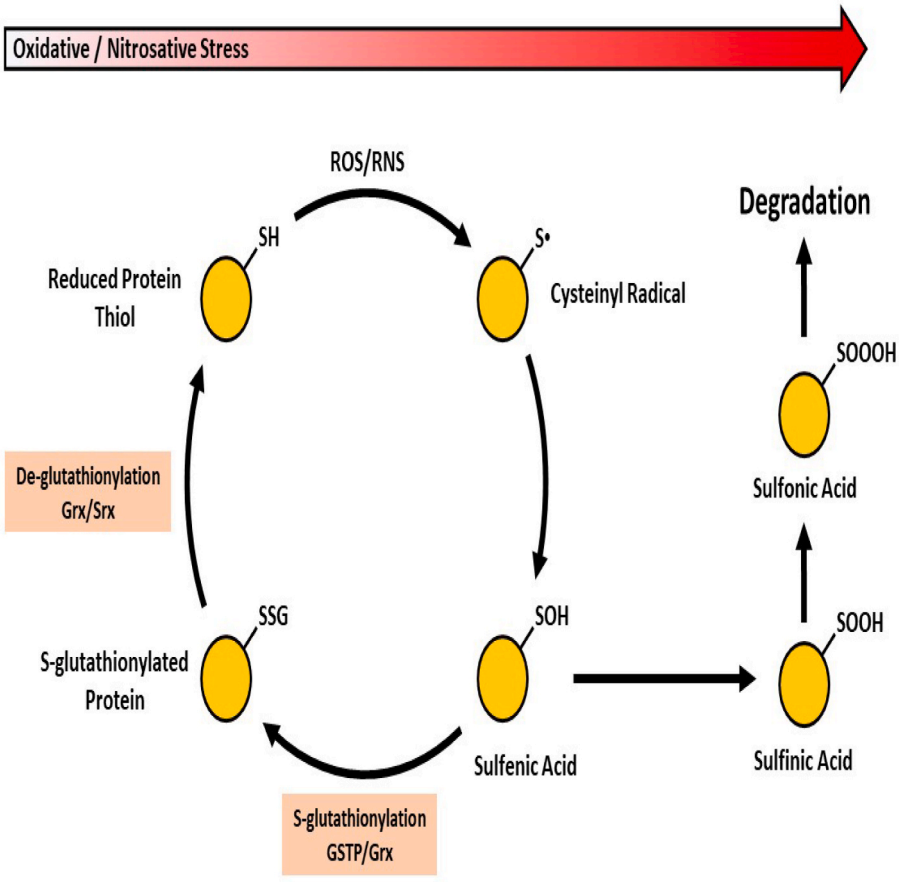


Fig. 5. Cycle of S-glutathionylation: Depiction of key phases in the S-glutathionylation cycle. This straightforward representation shows the stepwise changes in the oxidation states of sulfur. However, the oxidation of cysteine by reactive oxygen species (ROS) can occur through pathways involving either one or two electrons, leading to the simultaneous creation of cysteinyl radicals and/or sulfenic acids.

c-Jun phosphorylation, leading to the consequent triggering of downstream effectors. Under normal conditions, JNK1 catalytic action remains low, primarily because it is sequestered within a protein complex that includes at least GSTP and JNK [7]. Nevertheless, when exposed to oxidative damage, the GSTP:JNK complex separates, freeing GSTP for oligomerization and enabling JNK to initiate apoptosis subsequently (Fig. 4) [91,92]. The elevated presence of GSTP in numerous cancers might result from a developed reliance on the protein. As numerous kinases signalling cascade undergo dysregulation during proliferation, cancerous cells attempt to boost GSTP expression as a compensatory measure to regulate kinase activity.

Similarly, the GSTM1:ASK1 mechanism parallels the one suggested for GSTP:JNK. ASK1 initiates the JNK and p38 pathways, ultimately resulting in apoptosis induced by cytokine and stress [93]. In regular situations, ASK1 maintains low activity levels due to its association with GSTM1, culminating in the formation of a complex of GSTM1:ASK1. However, in stressed conditions, this complex disassembles, freeing and activating ASK1 [94,95]. During oxidative strain or heat shock, GSTM1 undergoes oligomerization, releasing ASK1, which consequently triggers apoptosis [94]. Consequently, an altered expression of GSTM1 has been linked to compromised clinical responses to therapy across various tumour types.

5.3. The role of GST in S-glutathionylation

There is widespread acknowledgment that addition of phosphate group stands as a pivotal protein modification, exerting a significant impact on cellular signalling and survival pathways. In this regard, there exists several similarities between the mechanisms of phosphorylation and S-glutathionylation. Certain microorganisms have the ability to flourish in phosphorus-deficient conditions by replacing sulfur, resulting in the formation of thiolipid membranes rather than phospholipid membranes [96]. The S-glutathionylation of phosphatases is integral for maintaining the recurring interplay between phosphorylation and dephosphorylation, offering an understanding of how the convergence of sulfur and phosphorus biochemistry may play a role in vital regulatory pathways. Many proteins subject to S-glutathionylation are key players in growth regulatory pathways, encompassing a range of kinases [97,98]. Therefore, within this framework, the S-glutathionylation cycle could introduce an additional level of regulation to the phosphorylation sequences typically overseen by kinases or phosphatases.

The S-glutathionylation occurrence is feasible when cysteines are situated in fundamentally crucial regions of the protein structure, such as those neighboring His, Arg, or Lys amino acids (Fig. 5) [99]. GST has the capacity to reduce the pKa of the cysteine thiol in GSH under physiological pH, culminating in the production of the nucleophilic thiolate anion (GS^-) [100]. The prompt supply of GSH in its activated state could dictate a specific GST catalytic or carrier role. Cysteines situated on the exteriors of globular proteins are available to both GSH and GSSG, making them susceptible to automatic S-glutathionylation [101]. These cysteines could be modulated using enzymes having reducing and deglutathionylating functions, such as thioredoxin (Trx), glutaredoxin (Grx) [102], and sulfiredoxin (Srx) [103].

5.4. Possible uses of bacteria GSTs

Bacterial GSTs participate in various chemical transformations, positioning them as adaptable tools with potential applications across diverse biotechnological realms. One notable application is in bioremediation, serving as a cost-effective alternative to conventional physicochemical methods for the cleanup of environmentally contaminated sites. The additional advantage lies in the straightforward genetic manipulations possible in bacteria and their rapid growth capabilities. Numerous investigations have explored the capabilities of GSTs, employing approaches that involve both purified proteins and the engineering of microorganisms. A summary of some of these studies is provided here. An instance of protein engineering utilizing the DNA blended approach was demonstrated by Kurtovic et al. [104]. They created hybrid enzymes by combining six alpha class GSTs from various mammalian sources, resulting in chimeric enzymes that exhibited enhanced catalytic properties and modified substrate preferences, particularly towards various harmful iodoalkanes. Another instance involves the development of fusion proteins with multiple distinct enzymatic functions [105]. This engineered chimeric enzyme proved to be efficient in eliminating ROS, indicating the potential applicability of this approach in medicine and environmental contexts.

Another possible use involves the creation of biosensors, which are detection systems extensively employed for monitoring polluted environments. Biosensors integrate a bio element with a detector component and are cost-effective, user-friendly, and known for their high sensitivity and selectivity. As an illustration, an optical biosensor for detecting captan in polluted waters was developed using a mammalian GST [106]. Captan is employed for managing a wide range of plant disease-causing microorganisms and acts as a potent suppressor of GSTs [107]. Bacterial GSTs, known for their high stability and diverse catalytic reactions, undoubtedly represent a valuable resource for the future.

5.5. GST application in plants

Several investigations have indicated the participation of GSTs in responses to biotic stress. A prior examination put forth a model delineating the manifold functions of plant GSTs in the interactions between plant hosts and pathogenic microbes, encompassing four scenarios: (i) resistance without visible symptoms, (ii) resistance associated with hypersensitive responses, (iii) constraining vulnerability to the systemic spread of pathogens and the death of plant cells/tissues, and (iv) fostering vulnerability to biotrophic fungi and viruses [108].

The initial genetically modified plants with enhanced GST capabilities were tobacco plants that exhibited heightened peroxidase activity due to the upregulated synthesis of an intrinsic Tau class GST, specifically Nt107. This upregulated synthesis led to increased GST and GPX action, rendering the transgenic plants more resilient to extremes in temperature, salt strain, and herbicide impact [109,110]. The expression of Nt107 in transgenic cotton plants resulted in elevated GST/GPX activity; however, these plants did not demonstrate an augmented resilience to oxidative strain factors, including salinity, low temperature, or exposure to the herbicides atrazine and imazethapyr [111]. The researchers posit that the integration of the foreign GST gene may interrupt the intrinsic strain adjustment system in cotton, resulting in a lack of defense against oxidative damage caused by stress [111]. Irrespective of the underlying factors, these results underscore the necessity for careful consideration in the design of transgenic organisms, emphasizing the essential inclusion of endogenous factors in the process.

Among the areas with the greatest potential within plant GST transgenesis lies the development of the capability to neutralize or remove foreign compounds like herbicides or contaminants. In specific species of crop like soybean and maize, GSTs play pivotal functions in shaping metabolism and selectivity crucial for controlling weeds without causing harm to the crop, of various herbicide classes. Nevertheless, in several other crops, the utilization of herbicidal agents is significantly limited due to the absence of the complete GST complement required for biotransformation. Specifically, tobacco and wheat are vulnerable to commonly employed thiocarbamate and chloroacetanilide herbicides. To address this limitation, maize GSTIV, classified under Phi class GST and highly effective against chloroacetanilide alachlor, was integrated into tobacco. The resulting transgenic plants displayed a noteworthy tolerance elevation to both thiocarbamate and chloroacetanilide herbicides [112].

Furthermore, transferring of GST genes into crops to confer resistance to crops' disease without yield penalty has been reported. Wang et al. (2020) found that introducing the GST gene (Fhb7) into wheat resulted in a consistently strong resistance to Fusarium head blight

(FHB). FHB is a fungal infection that severely impacts wheat production worldwide, leading to annual losses in the billions. In addition to reducing grain yield, the disease contaminates the grain with mycotoxins from the Fusarium pathogen, posing health risks to both humans and animals [113]. FHB is a major threat to global wheat production, yet limited resistance sources have been identified in wheat germplasm. Wang and colleagues cloned the FHB resistance gene Fhb7 by sequencing the genome of Thinopyrum elongatum, a species involved in wheat hybridization breeding. Fhb7 encodes a glutathione S-transferase (GST) that provides broad resistance to Fusarium by detoxifying trichothecenes via de-epoxidation. Notably, Fhb7 GST homologs are absent in plants, and evidence suggests *Th. elongatum* acquired Fhb7 through horizontal gene transfer (HGT) from an Epichloë species. Fhb7 introgression in wheat enhances resistance to both FHB and crown rot across various wheat backgrounds without affecting yield, offering a promising approach for Fusarium resistance breeding [113].

Phytoremediation, an emerging technology in bioremediation, involves the use of plants rather than bacteria to rapidly address soil and water pollution. The GSH–GST detoxification system is effective in eliminating various contaminants, including hazardous metals, radioactive substances, herbicidal agents, and diverse toxic organic compounds. However, certain compounds face challenges due to the absence of suitable bacterial or plant species or their diminutive accumulation/degradation efficacy [114]. In situations where the decontamination of soil, rather than water, is necessary, relying solely on bacteria may prove inadequate due to the slow or superficial nature of the detoxification process. In such instances, the utilization of high biomass plants with extensive root systems has been proposed as a viable tool for the rapid and effective elimination of heavy metals or noxious herbicidal residues from polluted soils. Tobacco plants, which have been genetically altered to incorporate the maize GSTF1 gene, demonstrated notably elevated resistance to alachlor in contrast to their non-transformed counterparts. These transgenic plants have the potential to be valuable for addressing herbicide-contaminated agricultural fields via phytoremediation [115].

6. Utilizing GST inhibition in the treatment of human diseases

The increased expression of GSTs in oncogenic tissues has been proven to enhance the cancer cells' resistance to chemotherapy through diverse mechanisms. Furthermore, the upsurge of GSTs has been indicated to play a crucial function in neurological disorders and pulmonary fibrosis. As a result, the investigation of specific inhibitors to target GST isozymes is being considered as a promising therapeutic strategy for a variety of diseases [116,117]. Over the course of several decades, inhibitors for GSTA, GSTP, GSTM, and GSTO have been discovered, with some already undergoing clinical investigation or therapeutic applications. The following outlines representative instances and advancements in research progress.

6.1. TLK199 and TLK177

Formulated for the management of myelodysplastic syndromes (MDS), Ezatiostat hydrochloride (TLK199) is a derivative of glutathione and functions as an inhibitor of GSTP1 [118]. TLK199 has demonstrated the ability to promote the transformation of precursor cells into fully developed granulocytes, monocytes, and erythrocytes. Additionally, it has the potential to hinder the formation of inefficient bone marrow in the context of MDS [119]. Functioning as an esterified prodrug, TLK199 goes through intracellular hydrolysis to produce the potent metabolite, TLK117. Notably, TLK117 specifically attaches and suppress GSTP1, displaying a Ki constant of 400 nM, which is markedly smaller relative to the Ki range of 20–75 nM observed for GSTA and GSTM [120]. By facilitating the phosphorylation of c-Jun by JNK, it activates the growth of normal hematopoietic cells and/or initiates the apoptotic eradication of cancerous cells [121]. Furthermore, TLK199 functions as an inhibitor of MDR1 and amplifies the impacts of concurrently administered anticancer medications influenced by efflux transport proteins [118,122]. Moreover, the inhibition of GSTP1 by TLK117 could equally impede pulmonary fibrosis through modulation of the JNK signaling cascade [117].

6.2. Auranofin

The orally administered antiarthritic drug, auranofin (AUF), which is a gold(I) phosphine compound [(2,3,4,6-tetra-*O*-acetyl-1-(thio-S)-α-D-glucopyranosato)(triethyl-phosphine)gold(I)], was initially unveiled for clinical use in 1979 [123]. Several research investigations have shown the potential of AUF and its analogs as effective antitumor medication, particularly in addressing carcinogenic formations including colorectal tumor and refractory sclerofibrosarcoma [124,125]. It has been documented that auranofin demonstrated suppressing impact on GSTP1 [126]. The inhibitory efficacy of auranofin on both GSTP1 wild-type and cysteine variant showed similarity, suggesting that, in contrast to other inhibitors, AUF's inactivation of GSTP1 is not associated with binding to cysteine residues. Further research focusing on elucidating the mechanisms behind AUF's inhibitory effects on GSTs is required.

6.3. Ethacrynic acid and its derivatives

First formulated in 1963, ethacrynic acid (EA) was designed as a powerful diuretic to address hypertension and intractable edema in patients [127,128]. EA was identified as a strong repressor of GSTA, GSTP, and GSTM enzymes, displaying the highest inhibitory action against GSTP1 [129]. The suppressing impact of EA on GSTP1 is ascribed to the presence of the α, β-unsaturated carbonyl group, that has the ability to form a covalent bond with cysteine residues within the GSTP1 active domain following Michael addition reaction [91]. It has been reported that EA exhibits anti-replicative actions on cancer cells and enhances the cytotoxic impact of various alkylating agents, including mitomycin C, melphalan, carmustine, and nitrogen mustard. Ethacrynic acid functions as both repressor and GSTs' substrate. Notably, the glutathionylated EA, EA-SG, demonstrated a 10-fold stronger suppressing efficacy against GSTP1 compared to EA [130]. Nevertheless, the clinical application of EA-GSH complex targeting GST is restricted owing to the absence of specificity and the pronounced diuretic adverse reactions [128,131]. Punganuru et al. [130] created a non-diuretic analog of EA, the EA-glucosamine conjugate (EAG) which specifically targets cancerous cells through the strongly expressed glucose transporter 1. Cellular survival tests revealed that EAG exhibited 3 to 4.5 times greater cytotoxicity against human malignant cells in comparison to EA. To address cisplatin resistance induced by GSTP1 overexpression, a trans-PtIV carboxylate conjugate named ethacraplatin (EA-CPT), incorporating ethacrynate, was formulated [132].

By merging the benefits of EA and cisplatin, this compound adeptly alkylates the DNA of cancerous cells and exhibits more effective inhibition of GSTP1 and GSTA1 compared to EA [133]. In a different investigation, the amalgamation of EA and a structure resembling flurbiprofen within the platinum complex PtCl2 (LEF) led to significant selectivity for cancer cells and successfully surmounted resistance to cisplatin [134].

6.4. NDBHEX and its derivatives

NDBHEX (6-(7-nitro-2,1,3-benzoxadiazol-4-ylthio) hexanol and its derivatives fall into a class of peptidomimetic compounds that are not related to glutathione (GSH). NBDHEX serves as a universal suppressor of GSTs, particularly effective suppressor of GSTP1. Apoptosis in cancer cell lines is induced by NBDHEX either independently or in conjunction with other anticancer agents such as doxorubicin, methotrexate, cisplatin, temozolomide and vincristine. The broad effectiveness of NBDHEX across cell lines from different tumors, including osteosarcoma, melanoma, leukemia, and small-cell lung cancers, depicts its

Table 1
Sources, functional characteristics and side effects of GST inhibitors.

S/N	Compounds	Sources	Functional characteristics	Side effects	References
1	TLK199 and TLK177	Pharmaceutical and Biotech Companies	Inhibition of GSTP, Redox homeostasis, hematopoiesis	cardiac-related side effects	[28,118, 146]
2	Auranofin	Pharmaceutical companies	Inhibits thioredoxin reductase and glutathione peroxidase, increases oxidative stress and apoptosis, indirectly affects GST functions via oxidative stress pathways	eryptosis, platelet dysfunction, and potential cardiotoxicity	[80,147, 148]
3	Ethacrynic acid and its derivatives	Pharmaceutical companies	Inhibition of GSTP1-1, generation of ROS species, activation of Caspase, downregulation of antiapoptotic proteins	diuretic activity, ototoxicity, liver damage, and bleeding complications	[130, 149–151]
4	NDBHEX and its derivatives	Pharmaceutical companies	potent inhibitor with low micromolar efficacy against GSTP1-1 and GSTM2-2 isoforms, formation of a stable sigma-complex between glutathione (GSH) and the inhibitor within the protein's active site, which disrupts the enzyme's function	hemolysis, nephrotoxicity, cell death (apoptosis) in healthy tissues	[152]

potential applicability across a wide range [135]. Various significant processes have been proposed to elucidate the cellular impacts of NBDHEX. Initially, the induction of apoptosis by NBDHEX is achieved through the stimulation of the signaling cascade of JNK/c-Jun [136]. Functioning as a GSTP1 suppressor, NBDHEX attaches to GSTP1's H site, prompting the liberation of GSTP1 from the JNK protein. Consequently, this initiates subsequent JNK phosphorylation, culminating in the halting of the tumor cell cycle and the provocation of apoptosis [137].

Additionally, it has been observed that NBDHEX disrupts the TRAF2-GSTP1 association in human osteosarcoma cells (U–2OS), leading to the activation of downstream signals such as JNK and p38, ultimately resulting in apoptosis [138]. Thus, NBDHEX was recommended as a prospective remedy for osteosarcoma of human origin that exhibits resistance to cisplatin [129]. Thirdly, research findings indicate that the compound has the capability not just to initiate various proapoptotic pathways but also to function as a suppressor of late-stage autophagy in melanoma. This dual role may contribute to tumor growth diminution, metastasis, and progression [139]. Finally, it's noteworthy that NBDHEX does not act as P-glycoprotein export pump substrate. Instead, it facilitates cysteine-triggered apoptosis in cells with elevated P-glycoprotein expression, suggesting its potential utility in the treatment of tumors that are P-gp positive [140]. Apart from its inhibitory effect on GSTP1, NBDHEX also displayed a strong binding affinity to GSTM2, potentially giving rise to adverse effects [141].

Furthermore, its limited water solubility poses a constraint on its oral bioavailability. Consequently, scientists have formulated various novel analogs of NBDHEX to address this solubility issue and enhance the selectivity for GSTP1. Three instances of these NBDHEX analogs, namely MC3165, MC3181, and MC2753, are highlighted as examples [142, 143]. Evidence indicates that both MC3165 and MC3181 showed improved solubility in aqueous environments, with MC3181 demonstrating greater selectivity for GSTP1 and increased cytotoxicity against osteosarcoma and melanoma cells [144,145]. These compounds demonstrated significant water solubility and potent suppressing action against GSTP1, thus presenting potential anti-proliferative effects on human melanoma and osteosarcoma cells. This implication suggests a potential clinical application for the treatment of melanoma.

The sources, functional characteristics and side effects of these described inhibitors are summarized in Table 1 below.

7. Conclusion and future perspectives

GSTs play a crucial function in detoxifying or metabolizing various chemical compounds, whether they originate from xenobiotic or endobiotic sources. The essential role of detoxification orchestrated GST is highlighted in xenobiotics tolerance, encompassing plant allelochemicals and artificially produced pesticides. Tolerance to a wide array of foreign compounds is facilitated by GSTs, achieved through chemical metabolism or sequestration, thereby providing protection against chemical-induced oxidative stress. The distinct roles of different GST classes can be attributed to their structural characteristics, particularly the makeup and spatial arrangement of amino acid residues within the catalytic cleft [153].

Advancements in this field in recent times have brought attention to the crucial role played by GST activities in diverse cellular processes and their ability to confer resistance to cancer treatment. Under this condition, it is not unexpected that numerous suppressors and pro-drugs aimed at GSTs have been produced and tried, with new structures or analogs emerging annually. Some of these compounds have advanced to clinical trials, suggesting the possibility of witnessing the approval of a GST suppressor or pro-drug for patient management in the coming years [154]. Most of the established and recently developed GST inhibitors have predominantly undergone assessment for their cytolytic impact in tumor cell lines and mouse xenotransplantation models, demonstrating encouraging effectiveness. However, a notable issue arises, particularly during in vitro testing of these drugs for their inhibitory properties, revealing a deficiency in specificity. Despite the often-crucial need to selectively target a specific GST isozyme or polymorphic form, achieving this goal with the currently synthesized and studied molecules has proven challenging. It is expected that the primary objective of future research in this field will be the pursuit of more precise GST inhibitors.

Funding

Dr. Aloke expresses gratitude to the Research Office of the University of the Witwatersrand, South Africa for providing postdoctoral funding.

CRediT authorship contribution statement

Chinyere Aloke: Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Olalekan Olugbenga Onisuru:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Ikechukwu Achilonu:** Writing – review & editing, Writing – original draft, Supervision, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

I acknowledge the effort of Keiran Mcinnes of Protein Structure-Function Research Unit, University of the Witwatersrand, South Africa for helping in drawing the Figures.

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