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REVIEW

Glutathione-S-transferases genes-promising predictors of hepatic dysfunction

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Abstract

One of the most commonly known genes involved in chronic diffuse liver diseases pathogenesis are genes that encodes the synthesis of glutathione-S-transferase (GST), known as the second phase enzyme detoxification system that protects against endogenous oxidative stress and exogenous toxins, through catalisation of glutathione sulfuric groups conjugation and decontamination of lipid and deoxyribonucleic acid oxidation products. The group of GST enzymes consists of cytosolic, mitochondrial and microsomal fractions. Recently, eight classes of soluble cytoplasmic isoforms of GST enzymes are widely known: α-, ζ-, θ-, κ-, μ-, π-, σ-, and ω-. The *GSTs* gene family in the Human Gene Nomenclature Committee, online database recorded over 20 functional genes. The level of GSTs expression is considered to be a crucial factor in determining the sensitivity of cells to a broad spectrum of toxins. Nevertheless, human *GSTs* genes have multiple and frequent polymorphisms that include the complete absence of the *GSTM1* or the *GSTT1* gene. Current review supports the position that genetic polymorphism of *GST* genes is involved in the pathogenesis of various liver diseases, particularly non-alcoholic fatty liver disease, hepatitis and liver cirrhosis of different etiology and hepatocellular carcinoma. Certain GST allelic variants were proven to be associated with susceptibility to hepatological pathology, and

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correlations with the natural course of the diseases were subsequently postulated.

Key Words: Glutathione-S-transferase; Non-alcoholic fatty liver disease; Drug induced liver disease; Liver cirrhosis

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Core Tip: Current review provide data regarding impact of genetic polymorphism of glutathione-S-transferase (*GST*) genes in the pathogenesis of various liver diseases, particularly non-alcoholic fatty liver disease, hepatitis and liver cirrhosis of different etiology and hepatocellular carcinoma. Certain GST allelic variants were proven to be associated with susceptibility to hepatological pathology and correlations with the natural course of the diseases were subsequently postulated.

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INTRODUCTION

Glutathione-S-transferases (GSTs) are group of phase II detoxification enzymes that catalyses the conjugation of glutathione (GSH) to a variety of endogenous and exogenous electrophilic compounds. It is without doubts that phase I enzyme reaction catalyses the incorporation of a functional group to a foreign compound, resulting in the formation of an intermediate metabolite. However, many of intermediates contain high potent chemical groups that can react with different cellular components including DNA, proteins and lipids[1,2]. This presence of intermediate metabolites can lead to multiple adverse health effects. Intermediate substances undergo phase II metabolism to form highly hydrophilic and less chemically active compounds, facilitating their excretion through bile or urine. Moreover, before being eliminated from the body, an extraneous compound can directly take part in phase II bypassing phase I detoxification. Phase II enzymes deactivate and detoxify foreign compounds unlike phase I enzymes which serves as activation metabolism, and therefore referred to as detoxification enzymes[3-5]. The aim of the current review was to overview up-to-date data and sum up results of own investigations regarding the distribution of *GST* genes polymorphisms, possible mechanisms of their involvement in the processes of desintoxication, drugs metabolism and cancerogenesis, and their role in the natural course of various liver diseases.

GSTs are presented by the cytosolic and membrane-bound microsomal super-family members. The groups of microsomal GSTs are structurally distinct from the cytosolic enzymes as they are rather homo-and heterotrimerise than dimerise in order to form a solitary active site. Microsomal GSTs are known to be the primary players in the endogenous metabolism of certain important substances like prostaglandins and leukotrienes. In contradistinction to microsomal GSTs, cytosolic GSTs are highly polymorphic and can easily be divided into eight sub-classes: α, μ, ω, π, θ, ζ, σ-, and ω-. The π and μ classes of GSTs play a regulatory role in the mitogen-activated protein kinase pathway participating in cellular survival and death signaling *via* protein-protein interactions with c-Jun N-terminal kinase 1 (JNK1) and apoptosis signal-regulating kinase (ASK1). JNK and ASK1 are in turn activated in response to cellular stress[6-8].

GSTs are broadly distributed in the living world, from single cell organisms like bacteria to various plants, animals, and humans. Plant GSTs include the φ, τ, θ, ξ and λ classes; the θ and ξ have analogues in animals, too. Moreover, the ξ and θ classes are numerous in non-vertebrate animals. Advocating that the ancestral progenitor for mammalian GSTs, probably arose from the θ class GSTs based on significant homology between the θ class GST and a dichloromethane dehalogenase enzyme from the prokaryote methylobacteriaceae, belonging to the genus of rhizobiales which is

known to be able to undergo genetic transformation and become competent for DNA uptake close to the end of the exponential growth phase[9-12].

The review of the GSTs gene family in the Human Gene Nomenclature Committee (HGNC), online database, shows 23 (as for beginning of 2021) functional genes contained within the group[13], which is a minor upgrade from the last decade, when there were only 21 of such genes reported. However, the number of subfamilies varies from 16 to 26 in different sources, and some genes of the group were determined as encoding membrane-bound enzymes having GST-like activity, but these genes are not related to the *GSTs* gene family evolutionarily. These genes include *GST-κ1* [glutathione S-transferase kappa 1 (*GSTK1*), *GST13*, HGNC: 16906, Chromosome 7q34], and microsomal glutathione S-transferase 1 (*MGST1*, Chromosome12p12.3) microsomal glutathione S-transferase 1-like 1 (prostaglandin E synthase-PTGES, *MGST-IV*, *PIG12*, *MGST1-L1*, *TP53I12*, HGNC: 9599, Chromosome 9q34.11), microsomal glutathione S-transferase 2 (*MGST2*, *MGST-II*, HGNC: 7063, Chromosome 4q31.1), and microsomal glutathione S-transferase 3 (*MGST3*, *GST-III*, HGNC: 7064, Chromosome 1q24.1). The known human *GSTs* gene family consists of six subfamilies-α (GSTA-alpha), μ (GSTM-miu), ω (GSTO-omega), π (GSTP-pi), θ (GSTT-theta) and ξ (GSTZ-zeta)[14].

Probably, naming of GSTs genes can cause confusion, because both GSTW and GSTO names are similarly used for GST omega (ω) subfamily marking, and GSTT or GSTQ are concurrently used for GST theta (τ) subfamily listing in different sources. The reason for this lack of certainty originates from the HGNC's rules. Moreover, quite similar nomenclature problems were reported with the mouse *GST* genes[14,15].

Nonetheless, while only human GSTs are of valid clinical significance, other *GSTs* genes are of notable interest as this may explain both the connections and developments of human GSTs. The soluble GSTs can be subdivided into the cytosolic and mitochondrial forms, only GSTκ is exclusively mitochondrial, while *GTSA1*, *4*, *GSTM1* and *GSTP1* encode both cytosolic and mitochondrial forms. The rest of the *GSTs* genes encode cytosolic proteins only. Note worthily, a vast number of GSTs were first identified in non-mammalian organisms, and were later recognised in humans and mammals[16-18], however most of the mammalian GSTs have been extensively studied and classified according to commonly assented criteria.

NON-HUMAN GSTS

Reports concerning plant GST enzyme revealed its involvement in catalysing the detoxification of the herbicide atrazine by conjugation to the endogenous γ-L-glutamyl-L-cysteinyl-glycine in sorghum and maize plants, which initiated a research that focuses on the detoxification of various herbicides and other toxic xenobiotic compounds in plants[19]. GSTs exhibit catalysis of the conjugation between various xenobiotics with electrophilic centres and the nucleophilic GSH, tagging the xenobiotic for vacuolar sequestration. The resulting γ-L-glutamyl-L-cysteinyl-β-alanine conjugates were much less toxic and more water-soluble than the original xenobiotics. It was shown that multiple plant GSTs participate in antioxidative protection due to their glutathione peroxidase activity[20].

The floral GSTs are mostly cytosolic and can represent up to 2% of soluble proteins. They have the ability to manifest auxin-inducibility and have ligandin function as well to participate in auxin transport. GSTs play a significant role during the normal metabolism of plant secondary products like anthocyanins[21]. The understanding of GSTs' role in endogenous floral processes and metabolic substrates had been still far from complete in contrast to the vast knowledge collected about their detoxification function[20,22].

Likewise, in human genome, floral GSTs enzymes are encoded by large gene families. The genome of the model plant Arabidopsis thaliana harbors 54 *GST* genes, which are grouped into seven distinct classes in plants. The well-studied large GSTF and GSTU classes are specific to plants, whilst the smaller GSTZ and GSTT classes exist in animal and human tissues. Lesser data is obtainable about the three outlying minor classes including GSTL, dehydroascorbate reductases, and tetrachloro-hydroquinone dehalogenase[21,23].

HUMAN GSTS

Human GSTs genes have multiple and frequent polymorphisms, including the complete absence (up to 20%-50% in some groups and populations) of the *GSTM1* or the *GSTT1* gene. The prevalence of the null genotype of *GSTT1* and *GSTM1* genes are heterogeneous amongst different ethnic populations. The *GSTT1* deletion is found in 20% of Caucasians and 80% of Asians[24]. While *GSTM1* zero genotype is detected in 38%-67% of Caucasian individuals, 33%-63% in East Asians and 22% to 35% in Africans and African Americans[25]. The substitution of adenine for guanine in nucleotide position 313 in the *GSTP1* gene leads to a reduction in the GST enzymatic activity which plays a significant role in the development of various diseases[26].

Following deficit in evident GSTs activities may lead to impaired detoxication of environmental substances, like toxins, carcinogens or drugs that may consequently generate clinically worth problems in patients lacking these genes[14,27-29].

GSTA, GSTM, and GSTP are over expressed in rat model of hepatic neoplasms (preneoplastic nodules) and the increased levels of these isoenzymes are assumed to provide the multidrug-resistant phenotype observed in these lesions. The majority of human tumors and human tumor cell lines express significant amounts of GSTP. The mechanisms responsible for over expression of GSTs, implicate transcriptional activation, stabilization of either messenger ribonucleic acid or protein, and gene amplification. In humans, remarkable interindividual differences are present in the expression of GSTA, GSTM, and GSTT. However, the exact molecular basis for the variation in GSTA is not known; missing of certain GSTM and GSTT classes can be attributed to deletion of the *GSTMI* gene in 50% of the population and deletion of the *GSTTI* gene in 16% of the population. The biological consequences of failure to express hGSTMI or hGSTTI protein can include higher susceptibility to some types of malignancies including skin, colon, bladder, and possibly lung cancer[10,30].

The level of GSTs expression is considered to be a crucial factor in determining the sensitivity of cells to a broad spectrum of toxins. The most abundant mammalian GSTs are the GSTA, GSTM and GSTP, however the biological control of these families is complex as they exhibit species-, age-, sex-, tissue-, and tumor-specific patterns of expression. Moreover, GSTs as shown above are regulated up and down by a broad spectrum of xenobiotics and drugs, with a significant number of these substances occurring naturally as non-nutritional components in modern food. It is obvious that humans are exposed regularly to such compounds[10].

Majority of chemical compounds, acting as GSTs inducers or inhibitors, have effect on transcriptional activation of *GSTs* genes through either antioxidant-responsive element, xenobiotic-responsive element, GSTP enhancer l, or glucocorticoid-responsive element[31,32].

The probability of GSTs is regulated *in vivo* by reactive oxygen species which is based on evidence that is not only but some of the most potent. GSTs inducers are capable of generating free radicals by redox-cycling, but hydrogen peroxide has been shown to strongly induce GSTs in plant and mammalian cells. An induction of GST by reactive oxygen species would appear to represent an adaptive response as GSTs detoxify some of the toxic peroxide-, carbonyl-, and epoxide-containing metabolites produced within the cell during oxidative stress[33-35].

Several functional studies of individual GSTs showed that they can positively contribute to host resistance against various microorganisms, whereas some physiologic mechanisms undergo further studying. Notwithstanding, the elevated total GST enzyme activities and notable accumulation of multiple GST transcripts and proteins was often observed in numerous host-pathogen interactions[23,36]. GSH is the most important non-protein thiol compound in several organisms and plays an important role in signaling and host defense reactions in infection. GSTs' participation in antioxidative react together with the crucial cellular antioxidant GSH in order to eliminate lipid hydroperoxides that accumulate in infected tissues, is clearly their distinguishable function[37-39].

Substantiation of *GSTs* genes from some commensals and parasites that may have immunomodulatory effect towards the immune system is growing, based on the involvement of separate profiles of cytokine gene transcription and different patterns of cell growth. Both antioxidants and oxidative stress manifest prompt transcription effect on many of the *GSTs* genes, which leads to increased protection of the cell against insult caused by environmental chemicals and drugs[40-42].

Possible interactions between host and microorganisms may result in three different ways: resistance gene (R-gene) mediated resistance, basal resistance and virulence. The first one (R-gene mediated), hypersensitive-type resistance is based on a specific interaction of a bacterial effect or gene product with the R-gene of the host organism.

R-gene mediated type of resistance is commonly corresponded with the localised cell death in infected host. It is unspecific, in case of basal resistance recognition; opposite to the R-gene mediated cell death, as genetically alien organisms are recognised based on their common molecular patterns. Induction of basal resistance is not associated with perceptible symptoms, in contrast to the hypersensitive-type R-gene mediated cell death. Poor host defense results in virulence[32,43].

Several members of the cytosolic GSTA, GSTM, GSTP, GSTT, microsomal transferases MGST2 and MGST3, are up-regulated by a wide spectrum of foreign compounds including but not limited to fumaric acid, thiazolidinediones, dexamethasone, phenobarbital, β-naphthoflavone, oltipraz, sulforaphane, coumarin, *etc.*[42]. The mechanism explaining this gene expression induction includes the aryl hydrocarbon receptor, and rostane receptor, the Pregnane X receptor, nuclear factor erythroid 2-related factor 2, CAATT/enhancer binding protein-β, and peroxisome proliferator-activated receptor-γ, which connects GSTs with other pathogenetic mechanisms, genes, and clinical conditions that include insulin resistance, diabetes mellitus type 2, arterial hypertension and abdominal obesity[44].

Due to the fact that GSTs play a determinative role in the detoxification of xenobiotics, their down- or up-regulation may obviously affect biological effects and metabolism of many biologically active compounds, industrials and environmental pollutants. Several studies have demonstrated the potency of some flavonoids to modify the expression of GSTs and their activities. Furthermore, real effect of flavonoid compounds on GSTs strongly hinge on concentration, remedy administration duration, chemical structure of particular flavonoid, as well as on GST origin and isoform. To add confusion, *in vitro* and *in vivo* studies results are often inconsistent, incongruous or conflicting. Notwithstanding, prudential use of a flavonoid enriched diets, which may potentially induce GSTs are commonly beneficial, however the uncontrolled intake of certain flavonoids like catechins and quercetin in high doses as a dietary supplement may threaten health in consequence of GST inhibition. Moreover, combined use of certain flavonoids with drugs (acetaminophen, cisplatine, cyclophosphamide, and simvastatin) or xenobiotics (acrylamide, isocyanates polycyclic aromatic hydrocarbons, and chlorpyrifos), which are GSTs substrates, might have significant pharmacological and toxicological consequences[45].

GSTs genes often, demonstrate high inductivity through various stimuli of both abiotic and biotic origin. For example, salicylic acid (SA) showed prompt inducible effect on multiple GSTs. Some of the *GSTs* genes (*GSTF2, GSTF8, GSTF10, GSTF11*) are recognised determining SA-binding receptor proteins, though the biological relevance of SA binding to these GSTs needs further study[36,46-48].

Similar behavior may be observed in other genes involving in hepato-pancreatic conditions like angiotensin-converting enzyme gene and peroxisome proliferator-activated receptors-γ gene[49]. We can presume, that there is little evidence of specific precise cellular hepatic alteration mechanisms resulted from GST enzymes dysfunction or corresponding genetics' dysregulations.

NONALCOHOLIC FATTY LIVER DISEASE

Due to the studies of possible difference in the distribution frequency of allelic variations in the *GSTP1* A313G polymorphism, it has been established that G allele is spread significantly and more frequent in patients with nonalcoholic fatty liver disease (NAFLD) than in healthy individuals ($\chi^2 = 5.69$, $P = 0.017$) in Ukrainian population (Table 1)[50]. This data is consonant with the results of Hashemi *et al*[51], who have demonstrated that G allele of *GSTP1* gene is a risk factor for NAFLD formation. It was investigated, that total bilirubin level in blood of NAFLD patients with GG genotype of A313G polymorphism of *GSTP1* gene was higher as compared to AA genotype and AG genotype carriers. Presence of G allele was also associated with increased alanin-aminotransferase activity, which was noticed to be significantly higher in NAFLD patients AG, and GG genotypes carriers as compared to patients with AA genotype [52].

Pro-and anti-inflammatory cytokines and adipokines profile varies in NAFLD patients with different polymorphic variants of the *GSTP1* gene (A313G) in particular. Homozygous patients with G allele are characterised by higher level of interleukin-10 (I1-10) in the blood as compared to patients with the AA and AG genotypes, that may occur potentially in response to the increase in the tumor necrosis factor-α (TNF-α) concentration, which proved the increased activity of inflammation processes[53,54]. NAFLD patients were investigated with low adiponectin levels in the blood in

Table 1 Distribution of polymorphic variants of the A313G polymorphism of the *GSTP1* gene in patients with nonalcoholic fatty liver disease and healthy individuals

Genotypes of the gene *GSTP1*	Patients with NAFLD, *n* = 104		Healthy individuals, *n* = 45	
	Absolute number, *n*	%	Absolute number, *n*	%
AA	47	45, 2%	28	62, 2%
AG	42	40, 4%	16	35, 6%
GG	15	14, 4%	1	2, 2%
A-allele	136	65, 4%	72	80, 0%
G-allele	72	34, 6%	18	20, 0%

NAFLD: Nonalcoholic fatty liver disease.

comparison with healthy people[55]. Moreover, according to Li *et al*[56] low adiponectin level is associated with the progression of steatohepatitis. The adiponectin concentration was lower in patients with NAFLD and AG and GG genotypes than in those with the AA genotype, indicating a worse adipokine profile for the NAFLD natural course[50]. A reverse tendency has been determined for leptin, however its blood level was higher in NAFLD patients with AG and GG genotypes as compared to those with the AA genotype[50]. This elevation of the leptin content in the *GSTP1* G allele carriers was, probably, associated with a high TNF-α concentration stimulating leptin production[57]. The aforementioned can prove the development of the leptin-resistance syndrome more severe in this cohort of patients[58]. In general, these observations indicate the formation of adipokine imbalance in the examined patients with AA genotype, which is typical for patients with NAFLD[59] which causes elevated leptin concentration against decrease adiponectin level in the blood[60].

Deletion polymorphic variants of *GSTT1* and *GSTM1* genes prevalence amongst NAFLD patients was approximately the same as their distribution between healthy individuals in Ukrainian population. These data are partially different from those suggested by Hori *et al*[61] who reported higher frequency of *GSTM1* null genotype in NAFLD patients as compared to control in the Japanese. There were not any notable differences in the parameters of the synthetic, detoxification, excretory liver functions together with activity of cytolytic and cholestatic syndromes and lipid profile in NAFLD patients with deletion of *GSTT1* and *GSTM1* genes and patients with functional allele of these genes[62]. It agrees with Rafiee *et al*[63] who also did not define importance contrasts in cholesterol and triglycerides plasma levels in individuals with different polymorphic variants of the studied genes. Interestingly, earlier studies of Maciel *et al*[64] suggested that double deletion genotypes of *GSTM1* and *GSTT1* genes were associated with hypertriglyceridemia.

Elevated TNF-α level in the blood is typical for NAFLD patients as compared to healthy individuals[65]. Jamali *et al*[66] proposed an algorithm involving TNF-α for predicting NAFLD/non-alcoholic steatohepatitis. Importantly, that null-genotype of *GSTT1* gene goes with higher TNF-α concentration as compared with patients having allele variant of *GSTT1*, and thereby indicate the activation of proinflammatory segment of cytokine profile and inflammatory processes[62]. Note worthily, TNF-α is one of the key factors involved in the insulin resistance, inflammation and apoptosis in case of NAFLD[67], thus its elevated level could be a predictor of aggravated liver injury in NAFLD patients with null-genotype of *GSTT1* gene.

Certain peculiarities in adipokine profile were detected regarding *GSTM1* genotype. Leptin plasma level was significantly higher in patients with null-genotype of *GSTM1* gene as compared to NAFLD patients with functional allele. This elevation of leptin content in null-genotype *GSTM1* carriers was probably associated with a high TNF-α concentration that stimulates leptin production[57]. Deletion polymorphism of *GSTT1* and *GSTM1* genes in patients with NAFLD was associated with lower content of restored glutathione, catalase activity. And in the case of carrier of zero genotype of *GSTM1* gene; it was also with higher level of reaction products of thiobarbituric acid in blood as compared to patients with functional allele of the gene[68].

DRUG INDUCED LIVER INJURY AND HEPATITIS

Prevalence of G allele of *GSTP1* (A313G) gene did not differ notably in chronic hepatitis patients in comparison with healthy individuals in Ukrainian population, however, presence of G allele was associated with higher activity of cytolytic syndrome lower restored glutathione blood content in comparison with patients AA genotype carriers[69]. *GSTP1* IIe/Val genotype was significantly more frequent in the patients with chronic hepatitis B infection and in patients with cirrhosis than in healthy individuals in Turkey; *GSTP1* Val/Val genotype was even more frequent in these patients[70]. In addition, these authors denoted relation between *GSTP1* gene polymorphism and hepatitis stage. In fact, as IIe/Val and Val/Val genotype frequencies increased so did the stages of the disease and tendency grow towards cirrhosis[70].

In our previous study, it was found that deletion genotype of *GSTM1* and *GSTT1* in patients with chronic hepatitis were representative to those in healthy individuals. Qi *et al*[71], have discovered that the genes *GSTM3* and *GSTP1* promoter methylation, which causes dysfunction of intracellular antioxidant defense system, more frequently occurs in patients with acute and chronic liver failure in case of hepatitis B virus, compared to patients with compensated viral hepatitis. Determination of methylated promoters of *GSTP1* and *GSTM3* genes can serve as a prognostic factor in the development of acute and chronic liver failure in these patients. It was found that *GSTO2* mutant genotypes were increased with progression, and the degree of hepatitis B virus (HBV) infection and the patients had mutant *GSTO2* genotypes such as (A/G, and G/G) were more susceptible for more severe HBV disease progression. The authors of the aforementioned study concluded that people with A/G and G/G genotype for *GSTO2* are more prone to develop hepatic failure[72]. Certain investigations have driven to the relation of *GST* gene polymorphism and drug induced liver injury. It was discovered almost twenty years ago, that homozygous null mutation at the *GSTM1* gene might predispose to hepatotoxicity for drugs used for the treatment of tuberculosis[73]. This statement was supported in the following studies reviling *GSTT1* homozygous null polymorphism may be a risk factor of antituberculosis drug-induced hepatotoxicity in Caucasians[74]. Meanwhile, presence of at least one functional allele of *GSTM1* was significantly more frequent amongst the groups with higher grades of liver toxicity for antituberculosis drugs in Brazilians[75]. Contrarily, G*STT1* and *GSTM1* were not related to increased antituberculosis drug induced liver injury in Indian citizens[76]. By now, certain researchers[77] have linked troglitazone intoxication in the development of chronic diffuse liver diseases with the double-zero genotype *GSTT1* and *GSTM1* genes, considering its consequence of insufficient activity of detoxification defense systems, low activity of conjugation of sulfuryl groups. It has been shown that the zero genotype of *GSTT1* gene increases the risk of drug-induced liver damage in particular, due to the use of isoniazid[78]. Finally, in meta-analysis, it was found that null *GSTM1* genotype was responsible for higher susceptibility to drug induced liver disease related to antituberculosis medications in East Asian population, but not the Indians or Caucasians[79]. There were no confirmed relationships between null genotype of *GSTT1* gene and this kind of drug induced liver disease[79]. On the other hand, Wu *et al*[80] investigated that patients with tuberculosis A allele carriers of *GSTP1* gene (A313G) have a higher risk of anti-tuberculosis drug-induced hepatotoxicity development.

LIVER CIRRHOSIS

With regards to the report of Burim *et al*[81] study of susceptibility to cirrhosis and pancreatitis in alcoholic, concerning the GST and cytochromes 450 genes polymorphism, revealed that *GSTP1* Val allele carriers were at higher risk of both diseases. Ghobadloo *et al*[82] discovered the association of cryptogenic cirrhosis with Val/Val *GSTP1* genotype which might be explained by low detoxification activity of protein that implicate this polymorphism as a risk factor for occurrence of the disease. Goncharova *et al*[83] showed that patients with liver cirrhosis AA genotype carriers have 2.5 times higher survival rate compared with the patients with the GG and AG genotypes of *GSTP1* gene.

Khan *et al*[84] showed an increase in risk to alcoholic cirrhosis in patients with *GSTM1* null genotype when compared with non-alcoholic or alcoholic controls. A much higher risk to alcoholic liver cirrhosis was observed in patients carrying combination of null genotypes of *GSTM1* and *GSTT1*[84]. The authors of the

mentioned study found interaction of GSTs with variant genotype of manganese superoxide dismutase, which detoxifies free radicals, or cytochrome P450 2E1 that generates free radicals, and resulted in several fold increase in risk to alcoholic liver cirrhosis. Thus, conclude the possible gene-gene interaction in modulating the risk of the alcoholic liver cirrhosis development[84]. However, in another study from Brazil, no differences were found in the prevalence of the *GSTM1* and *GSTT1* null genotypes between control non-alcoholics and alcoholics with liver cirrhosis, as well as alcoholics without disease and alcoholics with liver cirrhosis[81]. Several older studies also have got different conclusions regarding the impact of *GSTM1* null genotype on the appearance of liver cirrhosis in patients with alcohol abuse. Specifically, Harada *et al* [85] in Japanese and Savolainen *et al*[86] in Finland found an increased risk of liver cirrhosis associated with the GSTM1 null genotype in chronic alcoholics. Whilst, Frenzer *et al*[87] in Caucasian population and Rodrigo *et al*[88] in Spanish adults have not reported any. Brind *et al*[89] have found higher prevalence of zero *GSTT1* genotype in patients with alcoholic liver disease compared to patients who do not consume alcohol. Meanwhile *GSTT1* null genotype was not found to vary importantly between liver cirrhosis related to hepatitis B infection and healthy individuals[90]. At the same time, patients with *GSTM1* null genotype are at risk of progression of liver disease as the frequency of *GSTM1* null genotype was found to be significantly higher in chronic hepatitis B, hepatitis B cirrhosis and cryptogenic cirrhosis as compared with controls [90]. Moreover, the link between *GSTM1*, but not *GSTT1* null genotype and cryptogenic cirrhosis was found in Iranian population[82]. Komuro *et al*[91] in their investigations of primary biliary cirrhosis concluded that genotypic difference of *GSTM1* and *GSTT1* did not relate to susceptibility of this disease, nevertheless serum titer of anti-mitochondrial antibody of *GSTM1* null and *GSTT1* null patients were significantly higher than those of *GSTM1* positive and/or *GSTT1* positive patients. Baclig *et al*[92] also postulated that polymorphism in *GSTM1* null genotype seems to be associated with an increased risk of chronic liver disease amongst Filipinos.

HEPATOCELLULAR CARCINOMA

The GST null genotype has been examined to have an association with various malignancies including cancers of the bladder[93], gastric[94], colon[95], and lung[96]. K. Wu *et al*[97] investigated that *GSTP1* 313 G/G polymorphism is a strong predisposing risk factor for bladder cancer. Meanwhile, data regarding the role of *GST* gene polymorphism on the hepatocellular carcinoma (HCC) is sporicidal. Qu *et al*[98] have found single nucleotide polymorphism (SNPs) *GSTO2* rs7085725 and *GSTP1* rs4147581 were significantly associated with the overall survival of HCC patients and suggested to use them alone or in combination as potential prognostic markers for HCC patients. Particularly, according to the author's suggestion, SNP of *GSTP1* (rs4147581) could have a predictive biomarker in HCC patients aged ≤ 55 years[98]. *GSTM1* and *GSTT1* polymorphisms appear to be associated with a modest increase in the risk of HCC in Egyptian patients[99]. *GSTT1* null genotype was associated with more than 2-fold increased risk for HCC development in patients with hepatitis associated with hepatitis C virus (HCV) as compared to the control group. However, *GSTM1* null genotype was found to have a protective effect when hepatitis patients were considered in Indian population[100]. Meanwhile, in older study it was found that the *GSTT1*-null genotype alone did not affect risk of HCC development in HBV, but the *GSTM1*-null genotype was associated with a decreased risk for early-onset HCC[101]. The meta-analysis by Li *et al*[102], involving results of 46 related studies with more than 15 thousands of patients showed that both *GSTM1* null genotypes and *GSTT1* null genotypes increased the risk of HCC, while *GSTM1-GSTT1* dual-null genotypes increased the risk of HCC to a higher extend. Interestingly, during ethnicity consideration, this connection was significant only for Asians, and not for Caucasians and Africans. In older meta-analysis by Shen *et al*[103] *GSTM1* and *GSTT1* null genotype was found to be associated with higher risk of HCC with a similar ethnic pattern. GST-P1 rs1138272 (341C>T) polymorphism was found to have a protective effect on liver cancer development in a high-risk HCV/HBV-positive population in Caucasian ethnicity[104]. GST-P1 genetic polymorphisms (*i.e.*, Ile105Val, rs1695) were not associated with HCC risk in Asian population, European and African[105,106]. Higher *GSTP1* levels in tumor tissues indicated a better overall survival and disease-free survival for HCC patients[107]. The mentioned authors have found that *GSTP1* could decrease p-Akt in liver cancer cell lines and may inhibit alfa-fetoprotein expression. *GSTP1's* inhibition on cancer progression may be accomplished by arresting the cell

cycle at the G1/S transition in HCC cells[108]. *GSTA1* TT genotype was more frequent in HCC than in non-HCC patients, suggesting that individuals carrying this genotype could be associated with 2-fold higher risk of developing HCCs[109]. *GSTM1* and *GSTT1* null genotypes are associated with an increased HCC risk in Chinese population with higher risk typical for double null genotype. Furthermore, in another meta-analysis, it was investigated that null genotype of *GSTT1* was associated with HCC susceptibility in Asians, and both *GSTT1* and *GSTM1* genes deletion were associated with higher susceptibility. *GSTP1* Ile105 Val gene polymorphism was not correlated with this disease, however, polymorphisms in *GSTM1* and *GSTT1* genes are not related to the incidence of HCC in a high-risk Spanish population[110]. Marahatta *et al*[111] provided the support for the difference in genotypic distribution for GSTO1* A140D between hepatocellular carcinoma and cholangiocarcinoma.

CONCLUSION

Current review supports the position that genetic polymorphism of *GST* genes is involved in the pathogenesis of various liver diseases, specifically in non-alcoholic fatty liver disease, hepatitis and liver cirrhosis of different etiology and hepatocellular carcinoma. Certain *GST* gene allelic variants were proven to be associated with susceptibility to hepatological pathology and correlations with the natural course of the diseases were postulated. Still the data obtained in different studies sometimes is controversial and even conflicting. Thus, more investigations involving larger numbers of patients are needed.

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