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GLUTATHIONE –THE MASTER ANTIOXIDANT

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Glutathione, xenobiotics, tripeptide thiol.

Abstract

Oxidative stress plays a vital role in the development of alcoholic liver disease and has been associated with pathogenesis of non-alcoholic fatty liver disease (NAFLD).Oxidative stress is linked with many intensive care unit syndromes and diseases. Glutathione is an endogenously created tripeptide thiol with important biochemical and antioxidantproperties.GSH plays an important role in numerous basic cellular processes including protein synthesis, DNA synthesis and repair, cell proliferation, and redox signaling. GSH is consumed in phase-II metabolism of many drugs and xenobiotics. GSH is most concentrated intracellular antioxidant and has high electron-donating capacity. GSH has regenerative abilities not only for itself but for other antioxidants also (Vitamin A, C & E etc.) GSH is the only non-enzyme antioxidant that does not itself became a free radical after it has neutralized a free radical. Patients with alcoholic liver disease are known to have low hepatic and plasma GSH levels. Clinical trials with glutathione injectables have shown significant improvement of clinical signs and liver functions (e.g. SGOT, SGPT, serum bilirubin etc.) along with a good tolerance and safety in patients with alcoholic liver disease, NAFLD, Cirrhosis. Different clinical conditions where glutathione may be useful include burns, as a skin whitening agent, male infertility, Inherited GSH deficiencies ,diabetes mellitus, AIDS, pancreatic Inflammation, cancer chemotherapy/radiotherapy, neurodegeneration, Chronic hepatitis B, haemodialysis patients, acute respiratory distress syndrome (ARDS), systemic inflammatory response syndrome(SIRS), disseminated intravascular coagulation (DIC), multiple organ dysfunction, cardiovascular disease, trauma ischemia and reperfusion injury.

Introduction

Oxidative stress-Common denominator of multiple diseases

Reactive oxygen species (ROS)/oxygen free radicals are oxidizing mediators produced as by-products from the metabolism of oxygenFree radicals.[1] They contain 1 or more unpaired electrons in the outer orbit and are highly reactive and capable of damaging the cells.[1,2]Reactive oxygen mediate cell death by damaging DNA, cellular proteins and lipids.[2]Oxidative stress is a condition that reflects an imbalance between the production of ROS and a biological system's ability to readily detoxify the ROS or to repair the resulting damage.[1]

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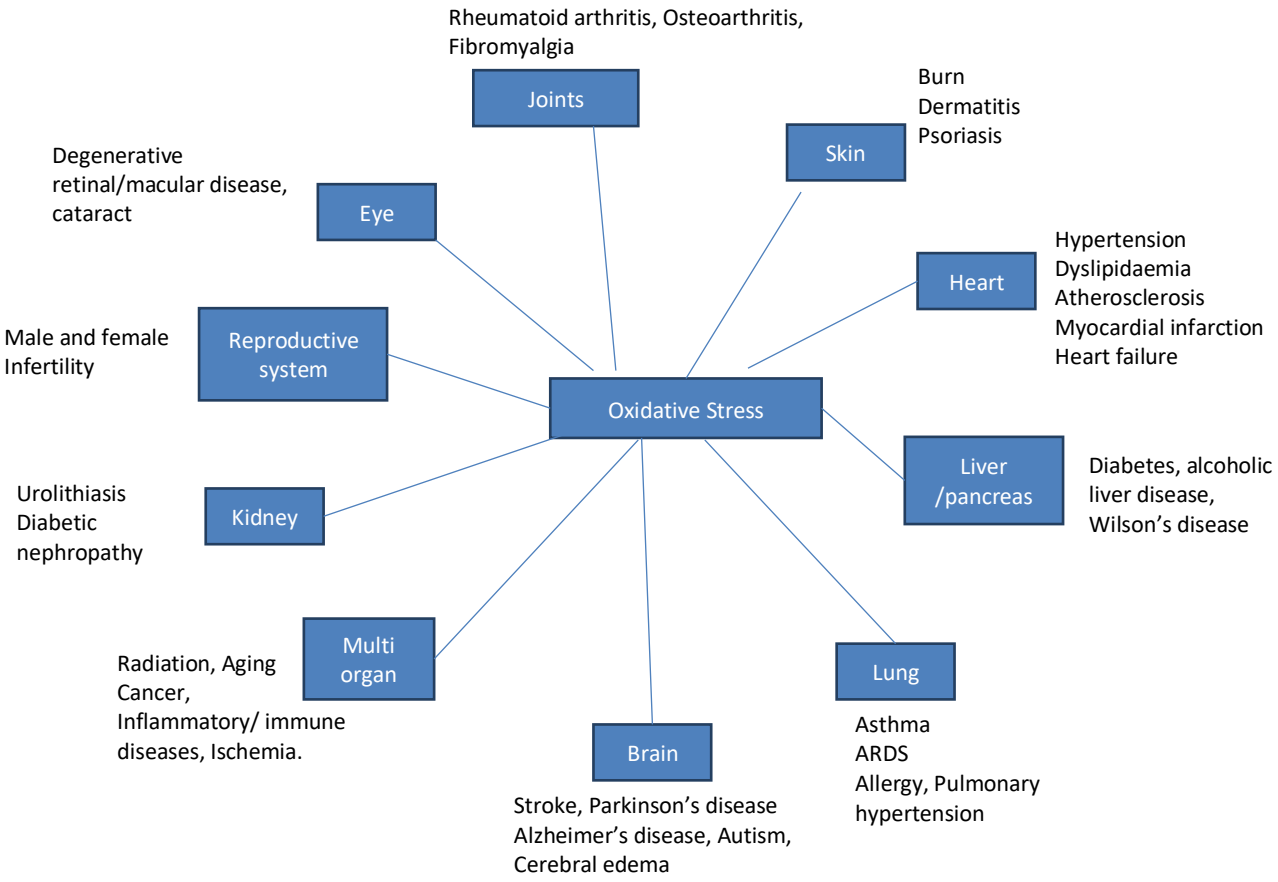
Consequences of oxidative stress[3, 4]



Intensive care unit syndromes and conditions linked to oxidative stress:

Oxidative stress is linked with many ICU syndromes and diseases.[5]

- ✓ Septic shock
- ✓ Acute respiratory distress syndrome (ARDS)
- ✓ Systemic inflammatory response syndrome(SIRS)
- ✓ Disseminated intravascular coagulation (DIC)
- ✓ Multiple organ dysfunction
- ✓ Burns
- ✓ Cardiovascular disease, liver failure, kidney failure
- ✓ Diabetes mellitus
- ✓ Trauma
- ✓ Ischemia and Reperfusion Injury
- ✓ Cancer

Antioxidants are the substances that can decrease the accumulation of free radicals by neutralizing them or countering their damaging effects on the cell. They are classified as follows.[1]

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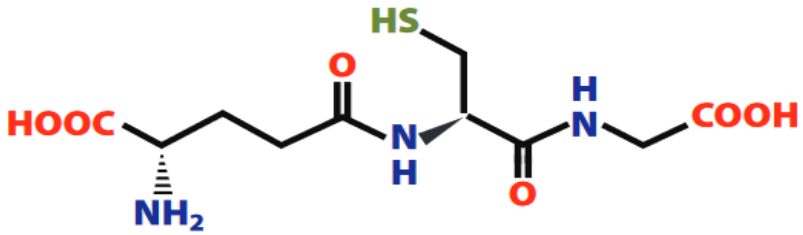
Enzymatic antioxidants	Non enzymatic antioxidants
Glutathione Peroxidases	Vitamin E
Superoxide dismutases	Vitamin C
Catalase	beta-carotene
Thioredoxin reductase system	Heme-binding proteins (ceruloplasmin, transferrin, haptoglobin, albumin)
Lipoamide system	

Glutathione: Mother of all antioxidants

Imagine a single item that could protect you against criminals, clean your house, wash your clothes, prepare food for you, and purify the air you inhale. While such a wonderful item doesn't exist in stores or online, it can be seen in every cell of the body. It's a tripeptide named glutathione and it is body's most powerful antioxidant.[7]



Reduced glutathione (GSH) is a linear tripeptide of L-glutamine, L cysteine, and glycine. First cysteine and glutamate are acted upon by gamma-glutamyl cysteinyl synthetase to synthesizegamma-glutamylcysteine. Second, GSH synthetase chains gamma-glutamylcysteine with glycine to generate GSH. As GSH levels rise, they self-regulate further GSH synthesis; otherwise, cysteine availability is usually rate-limiting. Fasting, protein-energy malnutrition, or other dietary amino acid deficiencies hamper GSH synthesis.[8]Glutathione exists in two forms GSH (Reduced form) & GSSG (Oxidised form).[7]Present naturally in all human cells, GSH is a water-phase orthomolecule. Its intracellular diminution ultimately leads to cell death and its clinical relevance has been researched for decades. GSH is the smallest intracellular thiol (–SH) molecule.6 GSH concentration in human tissues ranges from 0.1 to 10 millimolar (mM) with high concentration in the liver (up to 10 mM) and in the spleen, kidney, lens, RBC's, and leukocytes. Plasma level is in the micromolar range (approx. 4.5 μM). Factors that can lessen GSH include ultraviolet and other radiation; viral infections; environmental toxins, household chemicals, and heavy metals, inflammation, burns, septic shock and dietary deficiencies of GSH precursors and enzyme cofactors.[6]Glutathione differ from all of the other antioxidants in following aspects.[7]

- ✓ High electron-donating capacity (high negative redox potential).
- ✓ The most concentrated intracellular antioxidant.
- ✓ Regenerative abilities not only for itself but for other antioxidants also (Vitamin A,C & E etc.)
- ✓ Not only multifunctional antioxidant itself but is avital component of antioxidant enzymes including glutathione peroxidases.
- ✓ GSH is the only non-enzyme antioxidant that does not itself became a free radical after it has neutralized a free radical.

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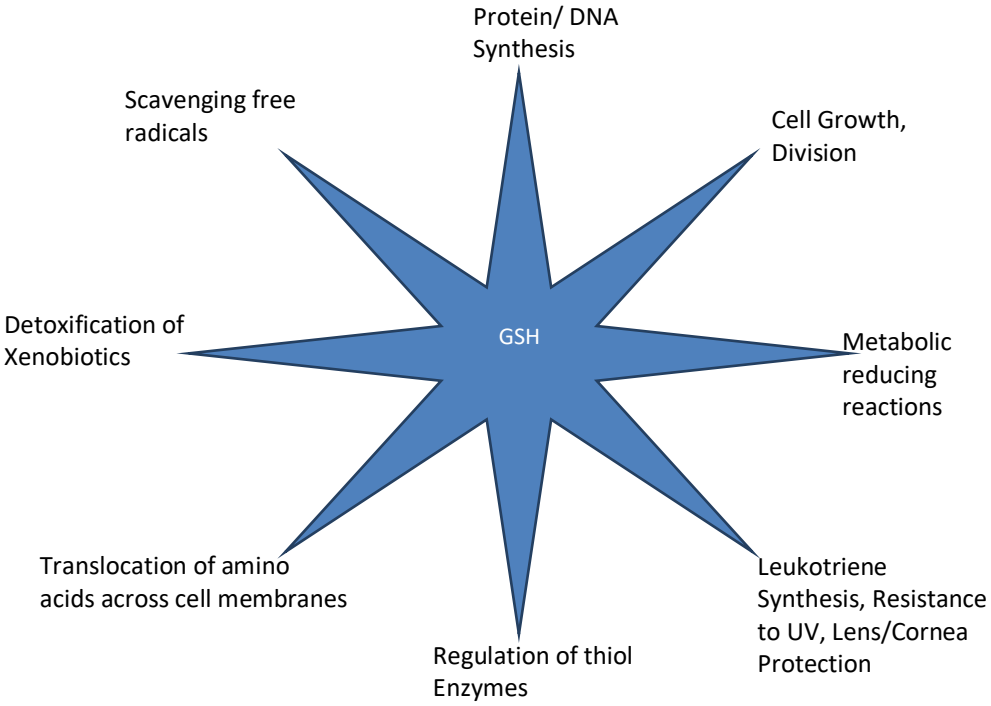
Important physiological functions of glutathione [9]



Issues with administration of amino acid precursors ie.2-0xo-thiazolidine-4-carboxylate/N-acetyl cysteine (NAC):

2-0xo-thiazolidine-4-carboxylate (OTC)-It is a compound in which the thiol group is masked and is converted to cysteine intracellularly by the action of 5-oxoprolinase. It has been used to raise cysteine levels in brain and has been shown to increase hepatic GSH levels. However, higher doses of OTC (0.45 mmol/ kg) were associated with side effects like pruritus, flushing, and drowsiness.[10]

N-acetyl cysteine (NAC)-It is a derivative of cysteine, has been used to boost GSH levels both in vitro and in vivo. Supplementation with NAC relies upon the body's ability to generate glutathione from available raw materials, an ability that decreases with age and in the presence of certain diseases, particularly liverdysfunction.[10]

Glutathione: Due to the action of an intestinal enzymeγ-glutamyl transpeptidase (GGT) which degrades GSH,GSH is poorly absorbed by oral route. Intravenous GSH has also been used as a means to augment GSH in various tissue compartments. In one study, GSH given intravenously at a dose of 600 mg only transiently (<1 hour) raised venous, lymph, and urine GSH levels with minimal effects on epithelial lining fluid GSH.[10]Advantages of IV administration of Glutathione are as follows[11]

- ✓ No drugmodification is required
- ✓ Effectively increases serum glutathione
- ✓ Minimal drug degradation
- ✓ Non-significant side effects

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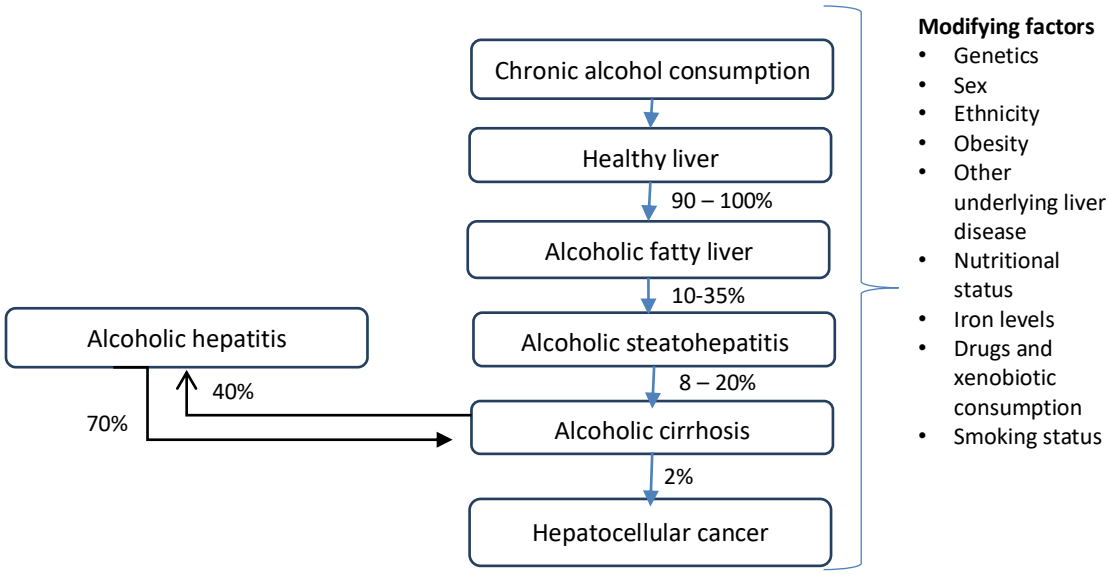
Clinical uses of Glutathione

Alcoholic liver disease (ALD)

It is one of the main causes of chronic liver disease worldwide. The disease can be caused by the chronic consumption of alcohol exceeding a certain daily amount, which varies significantly between the individuals.[12]Chronic, heavy alcohol consumption, is considered as the consumption of >40 g of pure alcohol per day (equating to 375 ml of 13 vol. % wine or >1 litre of 5 vol. % beer) over a sustained period of time (years). Howeverchronic consumption of even 12–24 g of alcohol per day has shown to increase the risk of cirrhosis (a late stage of ALD).[12]Risk factors that have been considered to be relevant to alcoholic liver injury and ALD include dose, pattern and duration of alcohol consumption, variety of alcoholic beverages, gender, ethnicity, obesity, hepatitis virus infection, genetic variability, and nutritional conditions.[13]

Epidemiology-Around 30% of total adultpopulation consumes alcohol. In India, 15 people die every day – or one every 96 minutes– from the effects of drinking alcohol. Mortality from alcoholic cirrhosis is declining in western nations but it is increasing in India.[14]The natural disease course of alcoholic liver disease is shown below.[12]



Pathogenesis of Alcoholic Liver Disease

Oxidative stress plays a pivotal role in the development of ALD.[15,16]Oxygen free radicals initiate lipid peroxidation, which leads to inflammation and fibrosis. Due to glutathione deficiency necrosis and apoptosis are exaggerated.[15]Oxidative mitochondrial damage directly causes liver cell death and favours alcohol-induced sensitization to the pro-apoptotic action of TNF-a.[16] The reactions of free radicals and lipid peroxidation products with hepatic proteins stimulate both humoral and cellular immune reactions and favour the breach of self-tolerance during ALD.[16] The involvement of free radical mechanisms in the pathogenesis of ALD is illustrated by the recognition of lipid peroxidation markers in the liver and the serum of patients with alcoholism.[16]

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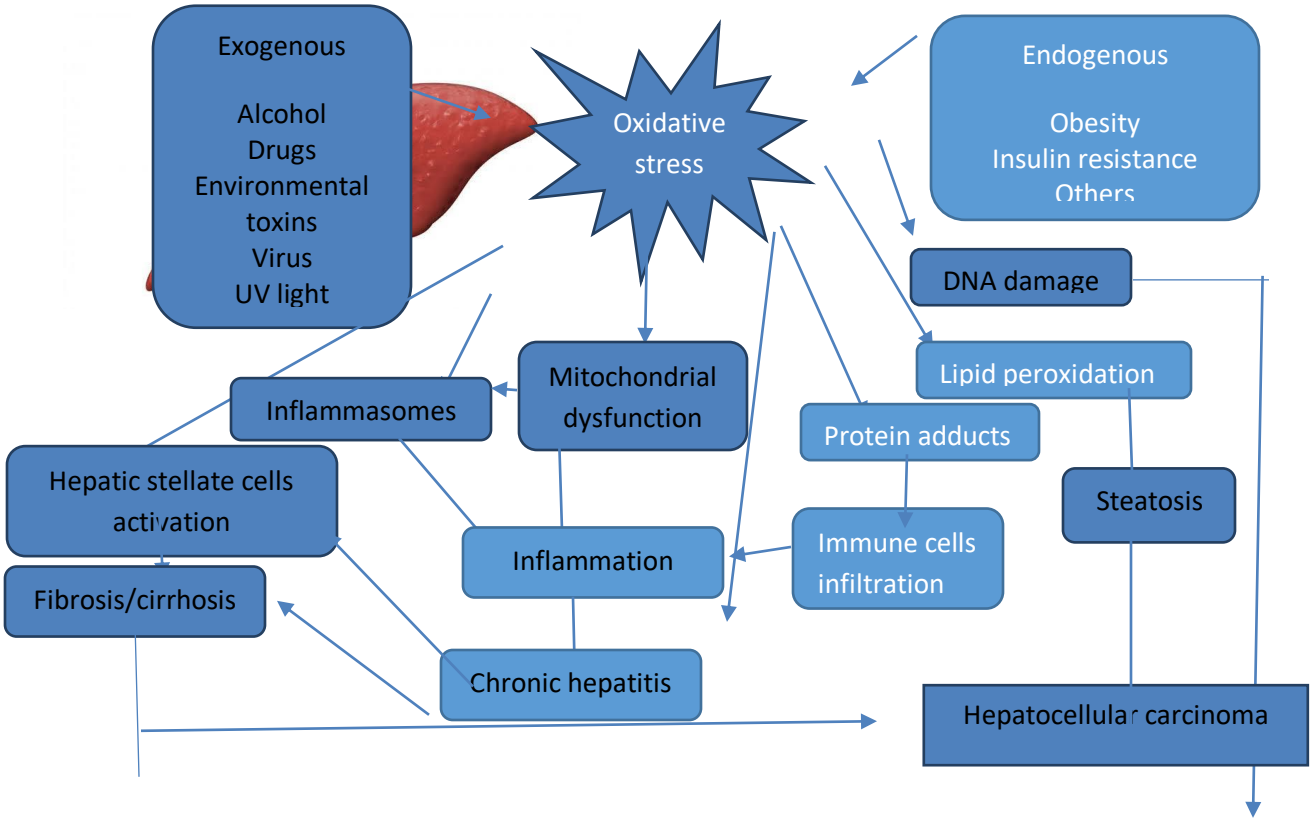
Fig. showing role of oxidative stress in liver disease[17]



Consequences of depleted mitochondrial GSH in chronic alcoholic liver disease

An important pathophysiological change in chronic alcoholic liver diseases is the selective diminution of hepatic mGSH pool by 45–60%.[18]mGSH depletion and the consequent raised production of mitochondrial reactive oxygen species subject hepatocytes to oxidative damage. The fallen level of mGSH also renders hepatocytes susceptible to TNF-α and FasL mediated cell death.[18]Alcohol-induced mGSH depletion is partially attributed to the reduced transport of GSH through the mitochondrial inner membrane. Alcohol stimulates lipid synthesis andhelps the deposition of cholesterol in the inner mitochondrial membrane.[18]

Rationale of glutathione therapy in alcoholic liver disease

Oxidant stress plays a key role in pathogenesis of liver disease & therefore antioxidants like glutathione is considered to be the important treatment options in ALD.[8]Depletion of hepatic glutathione (GSH) content in alcoholic liver diseases has been suggested to represent an important contributory factor to liver injury, and to enhanced morbidity related to liver dyfunction.[8]Role of GSH in liver P450 conjugation activity normally is quite considerable, accounting for upto 60% of all liver metabolites found in bile.[19] Factors that reduce the hepatic pool of GSH can decrease conjugation and enhance the toxicity of xenobiotics.[19]GSH is an extremely vital cell protectant. It directly quenches reactive free radicals.GSH/GSSG balance is critical to cellular homeostasis, stabilizing the cellular biomolecular spectrum, and facilitating cellular performance and survival.GSH availability down-regulates the pro-inflammatory potential of leukotrienes and other eicosanoids.[20]

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The approved indication for glutathione injection is for treatment of alcoholic liver disease (ALD) like alcoholic fatty liver, alcoholichepatitis, alcoholic liver fibrosis, and alcoholic liver cirrhosis.The dose of Glutathione injection is dependent on severity of the disease, in mild to moderate disease 600 mg -2400 mg twice daily by slow intramuscular or intravenous route.[20]After intramuscular administration of glutathione, rare instances of skin rash have been reported which have vanished after discontinuation of treatment. Mild pain at injection site has also been reported. As is the case with all intravenous infusions, febrile reactions, infections at site of injection, venous thrombosis or phlebitis and extravasation may occur.[20]Glutathioneinjection is contraindicated in the patients who show hypersensitivity to reduced glutathione.[20]

Clinical evidence on efficacy & safety of Glutathione Injection in hepatic diseases

Author	Study Design	Results
Bettini R 1993[21]	Prospective randomised trial Thirty patients with chronic alcoholic liver disease were treated with reduced glutathione (GSH) at a dose of 1800 mg/dayi.v. for 10 days, followed by 600 mg/die i.m. for further 20 days.	At the end of therapy, a significant reduction in serum hepatic enzymes was noted, in particular ALT and gamma-GT, together with a marked improvement in clinical symptoms. The efficacy (evaluated against a control group) and excellent tolerability confirm the use of GSH in this type of particularly common pathology.
Wang N 2008[22]	Randomized controlled trial N-acetyl cysteine (NAC)group (8 grams/day; 50 patients) vs GSH group (1.2 grams/day; 25patients). Duration28 days, evaluations made on day 0 and on days 7, 14, 21 & 28	Both NAC and GSH have therapeutic effects. The total effective rate was 84% in the NAC group and 72% in the GSH group. The rate of side effects was noted to be higher (13%) in the NAC group. GSH effectively reduces the level of serum total bilirubin andincreases prothrombin activity.
Zhang q 2000[23]	Randomized controlled trial 110 patients with ALD enrolled had a history of drinking over 80g-120g daily for 5yearsGroups GSH (infusion of 600g daily) or glutathione (with the same dosage, course and route asGSH) group. Treatment duration was for 30 days, evaluations made at 8th week.	The clinical signs were improved at a different degree in both groups. The efficacyrate observed with two GSH brands was 93%& 96% respectively. GSH shows a sound efficacy in the improvement of clinical signs and liver functions along with a good tolerance and safety.
Bresci G 1991[24]	Randomized controlled trial Patients: 80 patients with ALD Groups: 300 mg of reduced GSH or 10 mg of vitamin K Treatment duration: For 30 days, evaluations made at 30th day	At the end of the study all patients had improved, but the group treated with reduced GSH showed a greater improvement of liver function indices (AST,ALT, gamma-GT) which was statistically significant in comparison to that found inthe vitamin K treatment group ($p<0.05$). GSH was found to be superior to vitamin K supplement in the treatment of alcoholic liver diseases.
Wairokpam 2017[25]	Randomized case control study. Studypopulation consists of 100 patients with alcoholic hepatitis. Study population was divided into 2 groups of 50 patients each. One group was treated	Study results confirmed the good tolerability of glutathione. The administration of iv glutathione in alcoholic hepatitis showed the ability to significantly improve some indices of liver

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	with iv glutathione and the other group was treated conventionally without glutathione therapy	function and subjective complaints of patients

Other clinical conditions where glutathione can be useful

Condition/Disease	Comments
Multimorbidity development in older adults	Serum levels of GSH are inversely associated with multimorbidity development. GSH is a biomarker of multisystem dysregulation that ultimately leads to multimorbidity.[26]
Burns	Oxidative injury is one of the mechanisms responsible for the local and distant pathophysiological events observed after burn, and therefore anti-oxidant therapy might be beneficial in minimizing injury in burned patients.[27]Glutathione is one of the major buffer molecules of the cells and is known to increase the thermo resistance of the cells.[28]
As a skin whitening agent	Its skin-lightening effects due to direct as well as indirect inhibition of the tyrosinase enzyme and switching from eumelanin to phaeomelanin production.[29]
Male infertility	Glutathione exercised significant effect on sperm motility patterns.[30]
Inherited Deficiencies	Person with inherited deficiencies of the GSH-synthesizing enzymes exhibit limited or generalized GSH deficiency[31,32,33]with hemolytic anemia, spinocerebellar degeneration, peripheral neuropathy, myopathy, and aminoaciduria, and often develop severe neurological complications in the fourth decade of life. Low erythrocyte GSH also manifests in hereditary nonspherocytic lymphocytic leukemia, and glucose-6-phosphate dehydrogenase (G6PD) deficiency.[6]
HIV Infection	Oxidative stress is elevated at all stages of HIV disease.[6] HIV infection lowers GSH in the plasma, erythrocytes, T-cells and other lymphocytes, and monocytes.[34] Children with HIV also demonstrate low plasma GSH.[35] The cachexia and wasting of AIDS may be responsive to GSH repletion.[35]
Pulmonary Disease	GSH deficiency has been linked to various pulmonary diseases[31,33,35]including chronic obstructive pulmonary disease (COPD), acute respiratory distress syndrome (ARDS), neonatal lung damage, and asthma. ARDS patients with sepsis had low GSH and high GSSG in their epithelial lining fluid (ELF). GSH repletion can accelerate ARDS patient release from intensive care.[36]
Circulatory disorder	Intravenous glutathione prior to cardiopulmonary bypass surgery favourably influencedpostoperative renal function while improving systemic arterial function.[37]Infusion of GSH into patients with atherosclerosis enhanced microvascular vasodilation in response to acetylcholine, especially in subjects with baseline abnormal vessel wall reactivity.[38]The mechanism of vasodilation is suspected to be via glutathione's enhancement of nitric oxide.[6] In patients with peripheral artery disease, glutathione prolongs pain free walking

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	distance and shows an enhancement of macrocirculatory and microcirculatory parameters.[39]
Pancreatic Inflammation	Plasma GSH was significantly lowered in chronic pancreatitis linked to alcohol intake, and patients with acute pancreatitis responded well to glutathione repletion.[6]
Cancer chemotherapy/radiotherapy	GSH-enhancing strategies may improve the efficacy or tolerability of certain chemotherapy agentslike oxaliplatin,adriamycin, cyclophosphamide, and cisplatin.[6]In addition, the cells with higher levels of GSH carry more protection against radiation damage, thereby lessening the side effects of radiotherapy as well. GSH modulation represents a novel approach to the treatment and prevention of cancer.[6]
Neurodegeneration/Central Nervous System	Intravenous glutathione has been suggested empirically to improve Parkinson's disease symptoms of tremor and rigidity.[40]
Chronic hepatitis B	Glutathione treatment can improve liver function and inhibit inflammation and hepatic fibrosis in chronic hepatitis B patients.[41]
In hemodialysis patients	When reduced glutathione (were given to haemodialysis patients for 120 days, there was an increase in reduced glutathione levels in both RBC and plasma and an increase in haemoglobin, with a concomitant decrease in plasma oxidized glutathione and reticulocyte count in the GSH-treated alone group, After the first 3 months of therapy, anaemia improved significantly in 60% of the patients ,as long as they were undergoing therapy.[42]
Diabetes mellitus	Intravenous GSH infusion significantly increased both intraerythrocytic ratio and total glucose uptake in the same patients.[43]

Glutathione: Summary

Oxidative stress plays a vital role in the development of ALD and has been associated with pathogenesis of non-alcoholic fatty liver disease (NAFLD).[6]Glutathione is an endogenously created tripeptide thiol with important biochemical and antioxidant properties.[7]GSH plays an important role in numerous basic cellular processes including protein synthesis, DNA synthesis and repair, cell proliferation, and redox signaling. GSH is consumed in phase-II metabolism of many drugs and xenobiotics via glutathione S-transferase (GST)-mediated GSH conjugation reactions. Patients with alcoholic liver disease are known to have low hepatic and plasma GSH levels. Oxidative stress is one of the reasons that deplete GSH. Another is cysteine availability.[7] GSH appears to be particularly important in guarding mitochondria from xenobiotic- and ROS-induced toxicity.[6]Clinical trials with glutathione injectables have shown significant improvement of clinical signs and liver functions (e.g. SGOT, SGPT, serum bilirubin etc.) along with a good tolerance and safety in patients with alcoholic liver disease, NAFLD, Cirrhosis.[6]As per Guidelines of prevention and treatment for alcoholic liver disease(2018, China) reduced glutathione, which play their anti-oxidative, anti-inflammatory, and hepatocyte membrane or organelle protective roles on different degrees, can improve liver biochemical indices.[15]

References

1. Crimi E, Sica V, Williams-Ignarro S, Zhang H, Slutsky S, IgnarroJ et al. The role of oxidative stress in adult critical care. Free Radical Biology & Medicine.2006;40: 398–406.
2. Agrawal A, Durairajanayagam D, Halabi J, Peng J, Vazquez-Levin M. Proteomics, oxidative stress and maleinfertility. Reproductive Biomedicine Online.2014; 29:32-58.
3. Rahman T, Hosen I, Islam T, Shekha H. Oxidative stress and human health. Advances in Bioscience and Biotechnology.2012; 3(7A): 997-1019.

4. Goodwin T, Christofidou-Solomidou M. Oxidative stress and space biology: An organ-based approach. Int. J. Mol. Sci. 2018; 19:959.
5. Goodyear-Bruch C. Pierce D.Oxidative stress in critically ill patients. American journal of critical care. Nov 2002;11(6):543-553.
6. Monograph. Glutathione, Reduced (GSH). Alternative Medicine Review 2001; 6(6): 601-607.
7. Hyman M. Glutathione: The Mother of All Antioxidants. The Blog; 2011 [17/11/2017]. Available at: https://www.huffingtonpost.com/dr-mark-hyman/glutathione-the-mother-of_b_530494.html.
8. Franco R,Schoneveld J, Pappa A, PanayiotidisI. The central role of glutathione in the pathophysiology of human diseases. Archives of Physiology and Biochemistry. October/December 2007; 113(4/5): 234 – 258.
9. Kidd P.Glutathione: Systemic protectant againstoxidative and free radical damage. Alt Med Rev 1997; 2(3):155-176.
10. Alexander C, Thannickal V, Fanburg B. Glutathione deficiency in human disease Review Article.J.Nutr. Biochem.1994; 5(5):218–226.
11. MischleyL. Glutathioned efficiency in Parkinson's disease: Intranasal administration as amethod of augmentation. Journal of Orthomolecular Medicine.2011; 26(1):32-36.
12. Seitz H,Bataller R,Pinto H,Gao B,Gual A, Lackner C.Alcoholic liver disease. Nature reviews.Disease Primers.2018.4:16.
13. Li Y,Fan J. Guidelines of prevention and treatment for alcoholic liver disease(2018, China).Chinese Journal of Hepatology.2018;26(3):188-194.
14. World Health Organization. WHO country profile -India. 2010. [Last accessed on 19 Dec 2019) Availablefrom:http://www.who.int/whosis/whostat/EN_WHS10_Full.pdf?ua=1.
15. Ray S. Alcoholic Liver Disease (ALD).In APICON Medicine Update 2007.
16. AlbanoE. Alcohol, oxidative stress and free radical damage. Proceedings of the Nutrition Society.2006; 65:278–290.
17. Li S,Tan H, Wang N, Zhang Z, Lao L, Wong C et al. The Role of Oxidative Stress and antioxidants in liver diseases. Int. J. Mol. Sci. 2015; 16(11): 26087-26124.
18. Yuan L, Kaplowitz N. Glutathione in liver diseases and hepatotoxicity. Mol Aspects Med. 2009.Feb-Apr;30(1-2):29-41.
19. Pal P,Ray S.Alcoholic liver disease: a comprehensive review. European Medical Journal.EMJ. 2016;1[2]:85-92.
20. Prescribing information. Glutathione (MAXILIV 600MG IV/IM)
21. Bettini, R.; Azimonti, R.; Mairani, E.The use of reduced glutathione in alcoholic liver disease. Gazzetta Medica Italiana Archivio per le ScienzeMediche.1993;152(4): 117-120
22. Wang N, Shi XF, Guo SH, Zhang DZ, Ren H. A clinical study of N-acetylcysteine treatment inchronic hepatitis B patients. Zhonghua Gan Zang Bing ZaZhi. 2008 Jul; 16(7):487-9.
23. Zhang Q,Guo S, Hu D, He N, Zhang J, Zhong S et al. Effect of domestic glutathione on the alcoholic liver disease. Zhonghua Gan Zang Bing ZaZhi. 2000 Aug;8(4):239-40.
24. Bresci G, Piccinocchi M, Banti S. The use of reduced glutathione in alcoholic hepatopathy .Minerva Med. 1991 Nov;82(11):753-5.
25. Wairokpam T, Ningshen R, Niyas J, Nungsa S. Role of Intravenous Glutathione in Alcoholic Hepatitis. MSCR.2017; 05 (03): 18923-27.
26. Pérez M, Hooshmand B,Mangialasche F,Mecocci P,Smith AD,Refsum H. Glutathione serum levels and rate of multimorbidity development in older adults. J Gerontol A BiolSci Med Sci. 2019. Apr 25.doi: 10.1093/gerona/glz101.
27. Parihar A, Parihar MS, Milner S, Bhat S.Oxidative stress and anti-oxidative mobilization in burn injury.Burns. 2008 Feb;34(1):6-17.
28. Zor F, Ozturk S, Deveci M, Karacalioglu O, Sengezer M. Saving the zone of stasis: is glutathione effective?Burns. 2005 Dec; 31(8):972-6.

Volume 7 (Issue 2): February 2020 ISSN: 2394-9414
DOI- 10.5281/zenodo.3700161 Impact Factor- 4.174

29. Sonthalia S, Daulatabad D, Sarkar R. Glutathione as a skin whitening agent: Facts, myths, evidence and controversies. Indian J Dermatol Venereol Leprol 2016; 82:262-72.
30. Lenzi A, Lombardo F, Gandini L, Culasso F, Dondero F. Glutathione therapy for male infertility.Arch Androl. 1992 Jul-Aug; 29(1):65-8.
31. Sen CK. Nutritional biochemistry of cellular glutathione. Nutr Biochem 1997; 8:660-672.
32. Meister A, Larsson A. Glutathione synthetase deficiency and other disorders of the gamma-glutamyl cycle. In: Scriver CR, Kinzler KW, Valle D, et al, Eds. The Metabolic and Molecular Bases of Inherited Diseases. New York: McGraw-Hill;1995:1461-1477.
33. Gul M, Kutay FZ, Temocin S. Cellular and clinical implications of glutathione. Indian J ExpBiol 2000; 38:625-634.
34. Pace W, Leaf D. The role of oxidative stress in HIV disease. Free Rad Biol Med 1995; 19:523-528.
35. Anderson ME. Glutathione and glutathione delivery compounds. AdvPharmacol 1997; 38:65-78.
36. Suter P, Domenighetti G, Schaller M. N-acetylcysteine enhances recovery from acute lung injury in man. Chest. 1994; 105:190-194.
37. Amano J, Suzuki A, Sunamori M. Salutary effect of reduced glutathione on renal function in coronary artery bypass operation.J Am CollSurg 1994; 179:714-720.
38. Prasad A, Andrews P, Padder A.Glutathione reverses endothelial dysfunction and improves nitric oxide bioavailability.J Am Coll Cardiol. 1999; 34:507-514.
39. Arosio E, De Marchi S, Zannoni M, Prior M, Lechi A. Effect of glutathione infusion on leg arterial circulation, cutaneous microcirculation, and pain-free walking distance in patients with peripheral obstructive arterial disease: a randomized, double-blind, placebo-controlled trial.Mayo Clin Proc. 2002 Aug;77(8):754-9.
40. Otto M, Magerus T, Langland J. Use of Intravenous Glutathione for Symptom Management of Parkinson's disease: A Case Report. Alternative Therapies in Health and Medicine. Aliso Viejo. Jul/Aug 2018; 24(4): 56-60.
41. Qian Let al. Effects of reduced glutathione therapy on chronic hepatitis B.Cent Eur J Immunol. 2017; 42(1):97-100.
42. Santangelo F, Witko-Sarsat V, Drüeke T, Descamps-Latscha B. Restoring glutathione as a therapeutic strategy in chronic kidney disease. Nephrol Dial Transplant.2004 Aug; 19(8):1951-5.
43. De Mattia G, Bravi C, Laurenti O, Cassone-Faldetta M, Armiento A, Ferri C et al. Influence of reduced glutathione infusion on glucose metabolism in patients with non-insulin-dependent diabetes mellitus. Metabolism. 1998 Aug; 47(8):993-7