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Role of ELcor-GL Oral Solution for Liver, Pancreas & Gut Health

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ABSTRACT

The primary role of glutathione is to protect cells from oxidative stress. It is abundantly distributed in the mucosal cells of gastrointestinal tract both in animals and man. The highest concentration is found in the duodenum. The amount of glutathione ingested with foods, age and drug or ethanol consumption affect glutathione concentration. The detoxifying capability of glutathione is directly related to its thiol group and to its function as a substrate for enzymatic activity; in fact, glutathione regulates the action of glutathione-peroxidases and glutathione-transferases.

Glutathione is a tripeptide composed of glycine, cysteine and glutamine amino acids. These three amino acids are abundant in meat and poultry products and staple food such as rice. Cells in the body produce high amounts of glutathione, indicating that this molecule has a crucial role in the body. It is as important as cholesterol, glucose and potassium since all have similar levels in the cells. As a powerful antioxidant, it scavenges excess free radicals produced during cellular metabolism and chemical reactions. It neutralises these harmful free radicals, toxins and certain metals such as mercury. Glutathione exists in two forms: reduced glutathione (GSH), the active form of the tripeptide, and oxidised glutathione, the inactive state. Free radicals are not ordinarily harmful when produced in appropriate amounts. However, when found in excess, they can cause cellular damage and even cell death.

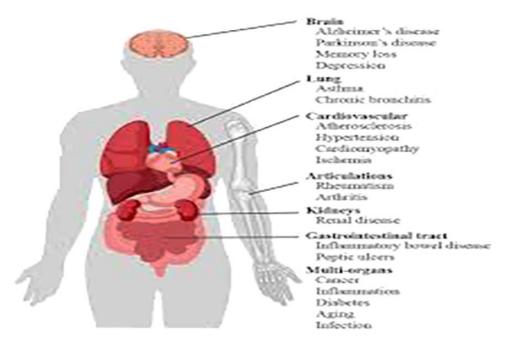
Glutathione reductase enzyme converts oxidised glutathione (the inactive form) to reduced glutathione. As long as glutathione reductase can cope with the conversion of oxidised GSH to reduced GSH, there will be no problem in neutralising free radicals. However, the problem lies when glutathione reductase is overwhelmed. When this occurs, levels of GSH become depleted, leading to an increased number of free radicals in the body. Since there is not enough reduced GSH to neutralise the free radicals, these radicals accumulate and can cause cellular damage. When low levels of GSH are prolonged, this can lead to constant cellular damage, leading to different diseases.

When a person ages, the number of GSH produced also reduces. This would explain why older people are more prone to diseases caused by chronic inflammation. Some of these diseases include GIT, type 2 diabetes, cardiovascular diseases and certain forms of cancer.

Keyword: ELcor-GL, Liver

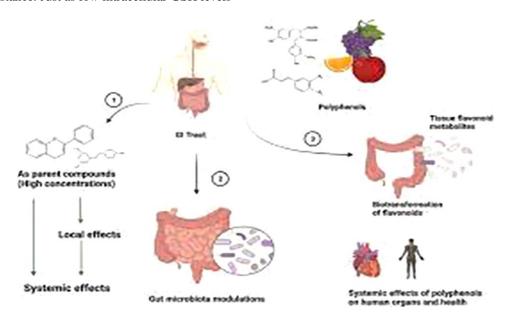
INTRODUCTION

Mechanism of Action of Glutathione (GSH)



Glutathione (GSH) plays important roles in antioxidant defense, nutrient metabolism, and regulation of cellular processes, including cell differentiation, proliferation and apoptosis. Glutathione deficiency contributes to oxidative stress, which plays a key role in aging and pathogenesis of many diseases, The GSH content is associated with multidrug and radiation resistance. Just as low intracellular GSH levels

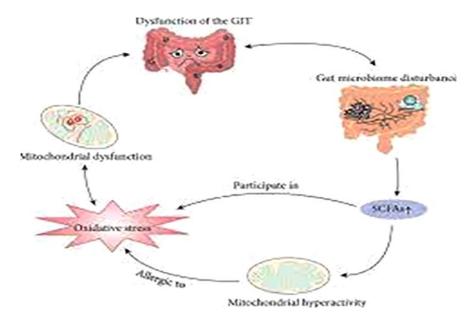
decrease cellular antioxidant capacity, elevated GSH levels generally increase antioxidant capacity and resistance to oxidative stress, and this phenomenon is observed in may cancer cells as compared to normal ones. The antioxidant role of ascorbate can also be important at the modulating immune cell functions.



The use of Glutathione for Liver, Pancreas & Gut Health

Glutathione, known as the mother of all antioxidants, should be definitely taken advantage of when it comes to enhancing the health of the liver, pancreas, and gut. But that is not all — Glutathione seems to be able to both efficiently prevent and treat various health issues linked to these organs including nonalcoholic fatty liver disease, acute pancreatitis, leaky gut syndrome, and irritable bowel syndrome.

Glutathione for liver health



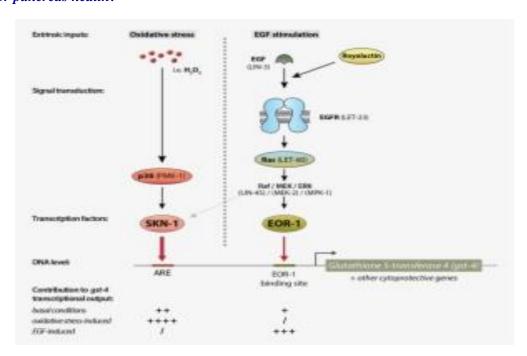
The powerful antioxidant abilities of Glutathione come in handy when it comes to liver health. Glutathione is able to reduce the levels of oxidative stress in the body, especially when it comes to the liver. By neutralizing the oxidative stress, Glutathione is protecting the liver from the common liver diseases which can be potentially life-threatening.

And when the liver disease does happen, such as nonalcoholic fatty liver disease, Glutathione supplements have been found beneficial in the treatment process, according to a study published in 2017. Nonalcoholic liver disease has been estimated to affect more than 100 million American adults. Glutathione supplements are able to reduce the cell damage in the liver, which can potentially lead to liver disease, by

stabilizing the antioxidant levels, especially the ones of Glutathione in the body, whose deficiency is considered to increase the risk of liver disease due to cell damage and death. Increasing the Glutathione levels can help not only to reduce the present damage but also, to prevent any further liver damage, which will contribute to an effective treatment.

For the purposes of enhancing the liver's health, Glutathione is meant to be given orally. As for patients who have been diagnosed with nonalcoholic fatty liver disease, its best approach is for Glutathione to be given intravenously in high dosages. Combined with serious lifestyle changes, Glutathione has been suggested to cause a significant improvement in the lives of these patients.

Glutathione for pancreas health?



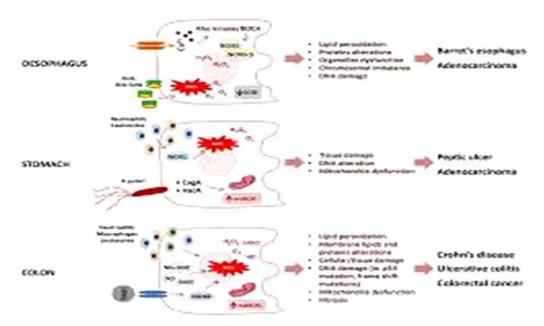
High levels of oxidative stress are known to harm the pancreas as well, increasing the risk of both acute and chronic pancreatitis. In fact, oxidative stress has been confirmed as a contributing factor for acute pancreatitis, pointing out the importance of antioxidants as a part of the treatment process of this serious health issue.

Since Glutathione, along with Vitamin C and Vitamin E, represent the best antioxidants that we can rely on, acute pancreatitis patients should be advised towards supplementing with all of the three important antioxidants. These antioxidants will efficiently reduce the levels of oxidative stress and free radicals in the body, thus improving

the overall health and preventing further health issues in the future to happen. By supplementing with Glutathione, individuals will be able to protect their pancreas and also treat these issues in the case that they do happen.

The best results have been achieved with Glutathione has been taken in combination with Vitamin C, for oral consummation. This, along with some serious lifestyle changes and proper therapy, has provided great results in the past. Although more research needs to be done, supplementing with Glutathione still presents itself as a valuable treatment method for acute pancreatitis.

Glutathione for gut health



Leaky gut syndrome, increasing the risk of multiple health issues, represents a medical condition that requires immediate attention. Luckily, researchers are coming up with new ideas on how to, not only treat but also prevent the leaky gut syndrome. The prevention and treatment of leaky gut syndrome include the use of Glutathione supplements.

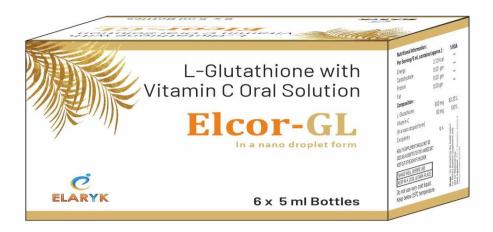
An enzyme, known as Glutathione peroxide, which is responsible for the strong antioxidant abilities of Glutathione, has been found helpful when it comes to protecting the gut walls and making them stronger. By strengthening the gut lining, Glutathione helps prevent the leaky gut syndrome, as a study published in Biochemistry has been telling us. Although the study has been done on animal subjects, and more research is required to be done on the topic, what we do know sounds promising enough.

But Glutathione can help patients with irritable bowel syndrome as well. It has been revealed that these patients have reduced activity of the enzymes which are involved in the synthesis of Glutathione. They have also been discovered to have lower levels of the main ingredient of Glutathione – cysteine, one of the three amino acids that combined represent Glutathione in the body.

By supplementing with Glutathione supplements, individuals will be able to strengthen their gut walls, and gut microflora, while acting to both prevent and treat the difficult digestive issues that are so commonly being diagnosed nowadays. For these patients, the best approach seems to be intravenous or topical use of Glutathione. However, the exact dosage is to be determined individually for each patient, taking in consideration different factors such as age, gender, overall health, medical history, etc.

COMPOSITION OF ELcor-GL Oral Solution

L-Glutathione- 500mg Vitamin C - 80mg



ROS and Human Diseases

Due to different roles of reactive oxygen species (ROS) in cell signaling and many human pathological processes, imbalance of GSH is observed in a wide range of pathologies, including cancer, neurodegenerative disorders, cystic fibrosis (CF), HIV, and aging (Townsend and Tew, 2003; Ganesaratnam *et al.*, 2004; Ken *et al.*, 2004; Hayes *et al.*, 2005). Maintaining proper GSH levels and oxidation state are important for cell function and their disruptions are observed in many human diseases. GSH deficiency leads to an increased susceptibility to oxidative stress and, thus,

progression of many disease states (Townsend and Tew, 2003; Ganesaratnam *et al.*, 2004; Ken *et al.*, 2004; Hayes *et al.*, 2005). On the other hand, elevated GSH levels increase antioxidant capacity and resistance to oxidative stress and this is observed in many types of cancer (Townsend and Tew, 2003; Ganesaratnam *et al.*, 2004; Ken *et al.*, 2004; Hayes *et al.*, 2005).

Free radicals produced by normal cellular metabolism can lead to extensive damage to DNA, protein, and lipid (Olinski *et al.*, 1992; Okamoto *et al.*, 1994; Devi *et al.*, 2000; Wu *et al.*, 2004).

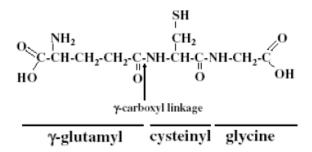


Fig 1: Structure of GSH or glutamylcysteinyl glycine.

The N-terminal glutamate and cysteine are linked by the carboxyl group of glutamate (Kaplowitz, et al., 1985).

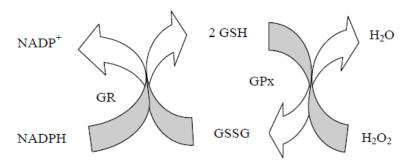


Fig 2: Pathway of ROS clearance (Adopted from Droge, 2002)

Oxidants such as H2O2 is converted to H2O by the action of GPX (or Catalase) using GSH. Regeneration of GSH requires NADPH and GR enzyme.

GR=glutathione reductase

GPx=glutathione peroxidase

DNA accumulates oxidative damage induced by ROS generated by endogenous and exogenous sources. This damage is a major contributor to diseases such as cancer, heart disease, cataracts, brain dysfunction, and aging (Ames, 1989; Ames, Shigenaga et al., 1993). It is estimated that the number of oxidative hits to DNA per cell per day is around 100,000 in the rat and 10,000 in the human (Ames, Shigenaga et al., 1993). It is possible that oxidative lesions in endogenous mammalian DNA exceeds 100 different types, of which 8-hydroxyguanine (8-oxoG) is one of the most abundant (Ames, 1989; Ames, Shigenaga et al., 1993). In normal functional cells, DNA repair enzymes efficiently remove most of the lesions formed by ROS. Several different methods are used to remove any mutation or mismatch (Demple and Harrison, 1994). In 2008, Petta et al., have shown the role of human DNA polymerase iota in protecting cells against oxidative stress (Petta et al., 2008). However, increased ROS generation in cancer cells leads to the accumulation of oxidative products of DNA, proteins, and lipids in tissues, and their release into the blood and urine. DNA oxidative products (8-oxoG), and lipid peroxidation have been detected in many cancer tissues, such as colorectal adenocarcinomas, mammary ductal carcinomas, renal cell carcinoma, and blood samples from leukemia patients (Olinski et al., 1992; Okamoto et al., 1994; Devi et al., 2000; Wu et al., 2004).

Glutathione, the powerful antioxidant abundantly produced by cells in the body, can play a critical role in improving gut health.

Glutathione has been lauded for its beneficial effects in improving skin elasticity, suppleness and strength. It is often used as a whitening product for men and women willing to have brighter and younger skin. However, do you know that it is not only limited to improving skin health? It is also the answer to common gut problems.

How does glutathione prevent oxidative stress?

Glutathione exists in two forms: reduced glutathione (GSH), the active form of the tripeptide, and oxidised glutathione, the inactive state.

Free radicals are not ordinarily harmful when produced in appropriate amounts. However, when found in excess, they can cause cellular damage and even cell death.

Glutathione reductase enzyme converts oxidised glutathione (the inactive form) to reduced glutathione. As long as glutathione reductase can cope with the conversion of oxidised GSH to reduced GSH, there will be no problem in neutralising free radicals.

However, the problem lies when glutathione reductase is overwhelmed. When this occurs, levels of GSH become depleted, leading to an increased number of free radicals in the body. Since there is not enough reduced GSH to neutralise the free radicals, these radicals accumulate and can cause cellular damage. When low levels of GSH are prolonged, this can lead to constant cellular damage, leading to different diseases.

What are the benefits of glutathione?

Glutathione has vast benefits for the body. Here are some examples of what glutathione can do for the body:

- Breaks down free radicals
- Eliminates heavy metals such as mercury that have entered the brain and other tissues
- Acts as cofactors of several enzymes
- Supports enzyme function
- Prevents chronic inflammation
- Supports the function of the mitochondria, the powerhouse of the cell
- Reduces lipid storage of fats in the liver
- Supports the elimination process of the body

What happens when you have glutathione deficiency?

Despite the ability of the body to produce glutathione naturally, depletion of glutathione can occur with increased age. Some people have deficient glutathione due to the inability of the glutathione reductase to convert oxidised glutathione to reduced glutathione, its active form.

When you have low levels of glutathione, you are more prone to develop the following diseases:

- Infectious diseases
- Certain forms of cancer
- Autoimmune diseases
- Chronic fatigue syndrome
- Parkinson's disease
- Cystic fibrosis
- Alzheimer's disease
- Diabetes
- Cardiovascular disease
- Neurodegenerative disease
- Metabolic syndrome
- Obesity

What are the factors that can deplete glutathione?

Several factors have been associated with the depletion of glutathione in the body. However, most of these factors can be avoided:

- Lack of sleep
- Chronic stress
- Tobacco use and smoking
- Air pollution
- Exposure to moulds and mycotoxins
- Accumulation of heavy metals from one's diet or inhalation of mercury
- Inflammation
- Diet high in foods that can cause inflammation, such as a diet high in sugar
- Genetics
- Ageing
- Excessive alcohol intake
- Inadequate intake of food rich in antioxidants, including glutathione

Can glutathione improve gut health?

Glutathione is labelled as the mother of all antioxidants. Hence, it is not unusual that glutathione can also improve gut health

In the gastrointestinal tract, glutathione is abundantly produced in the mucosal cells in both men and animals .

However, the highest concentration of GSH is found in the duodenum of the small intestine. The amount of GSH present in the food ingested, the person's age, alcohol, and drugs can influence the concentration of GSH in the duodenum.

The importance of GSH in the gut is highlighted by diseases formed when there is decreased GSH concentration in the gastrointestinal tract. In contrast, sufficient glutathione levels can lead to the healing and regeneration of the cells lining the gut.

Lower levels of glutathione concentration are directly related to damage to the intestine's mucosa. Further, when glutathione-related enzymes are depleted, these can increase the risk of cancer in the gastrointestinal tract.

Can glutathione manage leaky gut syndrome?

Glutathione peroxidase is an enzyme that converts oxidised glutathione to reduced glutathione. In the gut, glutathione peroxidase is necessary for increasing the levels of active glutathione. When levels of active glutathione are high, this is associated with a more robust gut lining.

A leaky gut is the progressive destruction of the gut lining and barrier. Here are some symptoms of a leaky gut:

- Headaches
- Joint pain
- Difficulty concentrating
- Fatigue
- Chronic diarrhoea, constipation
- Difficulty concentrating
- Confusion
- Skin problems

Glutathione can prevent a leaky gut by strengthening and protecting the gut walls. Hence, when you are struggling with the leaky gut syndrome, you can consult your doctor if it is safe for you to take glutathione. Your doctor can help you decide whether to take glutathione or other antioxidants to help treat your leaky gut.

What is the role of glutathione in managing irritable bowel syndrome?

The irritable syndrome is a common condition that affects the digestive system. Some of the symptoms of irritable bowel syndrome include the following:

- Bloating
- Stomach cramps
- Diarrhoea and constipation.

Symptoms of irritable bowel syndrome are often life-long. However, these symptoms can change over time. Irritable bowel syndrome can be managed successfully through proper treatment.

Although investigators have yet to determine the cause of irritable bowel syndrome (IBS), there are some potential cures or management strategies for IBS.

Depletion of glutathione reductase is linked with oxidative stress and developing IBS in the gastrointestinal tract . In contrast, when glutathione reductase levels are raised, symptoms of IBS also lessen. This study's findings revealed that glutathione could potentially treat or reduce the symptoms of IBS over time.

How can I naturally boost glutathione levels?

The good news is you can boost your glutathione levels by eating foods rich in glutathione or those that can increase GSH levels in the body. Here are some examples of food rich in glutathione or can increase levels of glutathione:

- Avocado
- Broccoli
- Okra
- Spinach
- Sulfur-rich foods such as:
- Leafy greens and arugula, asparagus, onions, garlic and eggs
- Vitamin C-rich foods such as citrus fruits and orange juice
- Almonds
- Baru almonds
- Sunflower seeds
- Brazil nuts
- Eggs
- Poultry meat
- Wild salmon
- Tuna
- Pasture-raised turkey

Eating these natural foods can boost that needed glutathione in your body! However, not all foods are created equal. Some foods have high levels of glutathione, and those that could only influence the production of glutathione in the body.

Are glutathione supplements safe?

The answer is yes! Glutathione is generally safe to use and has not been shown to lead to adverse events at dosages as high as 2000 mg/day.

Although the safety of glutathione is well established, there are still reported side effects and adverse events. These cases are few, and the side effects are often rare.

Examples of side effects include the following:

- Bloating
- Flatulence or passing of gas
- Stomach cramps
- Allergic reactions
- Bronchoconstriction leads to difficulties in breathing

It may not be advisable for patients with asthma to take inhaled glutathione due to isolated cases of asthma exacerbation

Another isolated case includes severe hepatic injury following intake of glutathione.

Adverse events are rare, while side effects are not expected. What is considered safe and effective for glutathione?

There have been studies demonstrating that glutathione can be taken as high as 2000 mg/day divided into three doses without any adverse events.

SUPPLEMENT FACTS

Presentation: ORAL SOLUTION Usage: As a food supplement.

Contra-indications: Product is contra-indicated in persons with Known hypersensitivity to any component of the product hypersensitivity to any component of the product.

Recommended usage: 5ML ORAL SOLUTION a day. "Do not exceed the recommended daily dose".

Administration: Taken by oral route at any time with food. Precautions: Food Supplements must not be used as a substitute for a varied and balanced diet in weight management program and in healthy lifestyle. This Product is not intended to diagnose, treat, cure or prevent any diseases. Do not exceed the recommended daily dose.

Warnings: If you are taking any prescribed medication or has any medical conditions always consults doctor or healthcare practitioner before taking this supplement.

Side Effects: Mild side effects like nausea, headache and vomiting in some individuals have been reported.

Storage: Store in a cool, dry and dark place.

CONCLUSION

Glutathione is a tripeptide composed of glycine, cysteine and glutamine amino acids. These three amino acids are abundant in meat and poultry products and staple food such as rice.

Cells in the body produce high amounts of glutathione, indicating that this molecule has a crucial role in the body. It is as important as cholesterol, glucose and potassium since all have similar levels in the cells. As a powerful antioxidant, it scavenges excess free radicals produced during cellular metabolism and chemical reactions. It neutralises these harmful free radicals, toxins and certain metals such as mercury. The liver, pancreas, and gut are all valuable organs whose health needs to be maintained within perfect ranges at all times. Glutathione, the powerful antioxidant that it is, is able to help us protect the health of these organs, but also, to treat some of the most difficult health issues that are happened regarding them as well. Glutathione can help patients with irritable bowel syndrome as well. It has been revealed that these patients have reduced activity of the enzymes which are involved in the synthesis of Glutathione. They have also been discovered to have lower levels of the main ingredient of Glutathione – cysteine, one of the three amino acids that combined represent Glutathione in the body. By supplementing with Glutathione supplements, individuals will be able to strengthen their gut walls, and gut microflora.

REFERENCES

- 1. Ames BN. Endogenous oxidative DNA damage, aging, and cancer. Free Radic Res Commun. 1989;7(3-6):121-8. doi: 10.3109/10715768909087933, PMID 2684796.
- 2. Ames BN, Shigenaga MK, Hagen TM. Oxidants, antioxidants, and the degenerative diseases of aging. Proc Natl Acad Sci U S A. Proceedings of the National Academy of sci of the united states of Am. 1993;90(17):7915-22. doi: 10.1073/pnas.90.17.7915, PMID 8367443.
- 3. Arrigo AP. Gene expression and the thiol redox state. Free Radic Biol Med. 1999;27(9-10):936-44. doi: 10.1016/s0891-5849(99)00175-6, PMID 10569626.
- 4. Behrend L, Henderson G, Zwacka RM. Reactive oxygen species in oncogenic transformation. Biochem Soc Trans. 2003;31(6):1441-4. doi: 10.1042/bst0311441, PMID 14641084.
- 5. Blair SL, Heerdt P, Sachar S, Abolhoda A, Hochwald S, Cheng H et al. Glutathione metabolism in patients with non-small cell lung cancers. Cancer Res. 1997;57(1):152-5. PMID 8988057.
- 6. Carney DN, Mitchell JB, Kinsella TJ. *In vitro* radiation and chemotherapy sensitivity of established cell lines of human small cell lung cancer and its large cell morphological variants. Cancer Res. 1983;43(6):2806-11. PMID 6303568.
- 7. Clark EP, Epp ER, Biaglow JE, Morse-Gaudio M, Zachgo E. Glutathione depletion, radiosensitization, and misonidazole potentiation in hypoxic Chinese hamster ovary cells by buthionine sulfoximine. Radiat Res. 1984;98(2):370-80. PMID 6539482.
- 8. Cullen KJ, Newkirk KA, Schumaker LM, Aldosari N, Rone JD, Haddad BR. Glutathione S-transferase {pi} amplification is associated with cisplatin resistance in head and neck squamous cell carcinoma cell lines and primary tumors. Cancer Res. 2003;63(23):8097-102. PMID 14678959.
- 9. Demple B, Harrison L. Repair of oxidative damage to dna: enzymology and biology. Annu Rev Biochem. 1994;63(1):915-48. doi: 10.1146/annurev.bi.63.070194.004411, PMID 7979257.
- 10. Devi GS, Prasad MH, Saraswathi I, Raghu D, Rao DN, Reddy PP. Free radicals antioxidant enzymes and lipid peroxidation in different types of leukemias. Clin Chim Acta. 2000;293(1-2):53-62. doi: 10.1016/s0009-8981(99)00222-3, PMID 10699422.
- Dröge W. Free radicals in the physiological control of cell function. Physiol Rev. 2002;82(1):47-95. doi: 10.1152/physrev.00018.2001, PMID 11773609.
- 12. Ganesaratnam K, Balendiran DR, Fraser D. The role of glutathione in cancer. Cell Biochem Funct. 2004;22(6):343-52.
- 13. Goodwin G, Baylin SB. Relationships between Neuroendocrine Differentiation and Sensitivity to {gamma}-radiation in culture line oh-1 of human small cell lung carcinoma. Cancer Res. 1982;42(4):1361-7. PMID 6120760.
- 14. Griffith OW, Anderson ME, Meister A. Inhibition of glutathione biosynthesis by prothionine sulfoximine (S-n-propyl homocysteine sulfoximine), a selective inhibitor of gamma-glutamylcysteine synthetase. J Biol Chem. 1979;254(4):1205-10. doi: 10.1016/S0021-9258(17)34188-1, PMID 33187.
- 15. Guichard M, Lespinasse F, Malaise EP. Influence of buthionine sulfoximine and misonidazole on glutathione level and radiosensitivity of human tumor xenografts. Radiat Res. 1986;105(1):115-25. doi: 10.2307/3576731, PMID 3945723.
- 16. Hassan HM, Fridovich I. Mechanism of the antibiotic action pyocyanine. J Bacteriol. 1980;141(1):156-63. doi: 10.1128/jb.141.1.156-163.1980, PMID 6243619.

- 17. Hayes JD, Flanagan JU, Jowsey IR. Glutathione transferases. Annu Rev Pharmacol Toxicol. 2005;45(1):51-88. doi: 10.1146/annurev.pharmtox.45.120403.095857, PMID 15822171.
- 18. Hu Y, Rosen DG, Zhou Y, Feng L, Yang G, Liu J et al. Mitochondrial manganese-superoxide dismutase expression in ovarian cancer: role in cell proliferation and response to oxidative stress. J Biol Chem. 2005;280(47):39485-92. doi: 10.1074/jbc.M503296200, PMID 16179351.
- 19. Irani K, Xia Y, Zweier JL, Sollott SJ, Der CJ, Fearon ER et al. Mitogenic signaling mediated by oxidants in ras-transformed fibroblasts. Science. 1997;275(5306):1649-52. doi: 10.1126/science.275.5306.1649, PMID 9054359.
- 20. Kaplowitz N, Aw TY, Ookhtens M. The regulation of hepatic glutathione. Annu Rev Pharmacol Toxicol. 1985;25(1):715-44. doi: 10.1146/annurev.pa.25.040185.003435, PMID 3890714.
- 21. Kawanishi S, Hiraku Y, Pinlaor S, Ma N. Oxidative and nitrative DNA damage in animals and patients with inflammatory diseases in relation to inflammation-related carcinogenesis. Biol Chem. 2006;387(4):365-72. doi: 10.1515/BC.2006.049, PMID 16606333.
- 22. Higashi K, Hiai H, Higashi T, Muramatsu M. Regulatory mechanism of glutathione S-transferase P-form during chemical hepatocarcinogenesis: old wine in a new bottle. Cancer Lett. 2004;209(2):155-63. doi: 10.1016/j.canlet.2004.01.003, PMID 15159017.
- 23. Komatsu D, Kato M, Nakayama J, Miyagawa S, Kamata T. NADPH oxidase 1 plays a critical mediating role in oncogenic Ras-induced vascular endothelial growth factor expression. Oncogene. 2008;27(34):4724-32. doi: 10.1038/onc.2008.102, PMID 18454179.
- 24. Nishikawa M. Reactive oxygen species in tumor metastasis. Cancer Lett. 2008;266(1):53-9. doi 10.1016/j.canlet.2008.02.031, PMID 18362051.
- 25. Mattson DM, Ahmad IM, Dayal D, Parsons AD, Aykin-Burns N, Li L et al. Cisplatin combined with zidovudine enhances cytotoxicity and oxidative stress in human head and neck cancer cells via a thiol-dependent mechanism. Free Radic Biol Med. 2009;46(2):232-7. doi: 10.1016/j.freeradbiomed.2008.10.023, PMID 18983911.
- 26. Meister A, Anderson ME. Glutathione. Annu Rev Biochem. 1983;52(1):711.
- Okamoto K, Toyokuni S, Uchida K, Ogawa O, Takenewa J, Kakehi Y et al. Formation of 8-hydroxy-2-deoxyguanosine and 4-hydroxy-2-nonenalmodified proteins in human renal-cell carcinoma. Int J Cancer. 1994;58(6):825-9. doi: 10.1002/ijc.2910580613, PMID 7523311.
- 28. Olinski R, Zastawny T, Budzbon J, Skokowski J, Zegarski W, Dizdaroglu M. DNA base modifications in chromatin of human cancerous tissues. FEBS Lett. 1992;309(2):193-8. doi: 10.1016/0014-5793(92)81093-2, PMID 1324197.
- 29. Oltra AM, Carbonell F, Tormos C, Iradi A, Sáez GT. Antioxidant enzyme activities and the production of MDA and 8-oxo-dG in chronic lymphocytic lerkenia. Free Radic Biol Med. 2001;30(11):1286-92. doi: 10.1016/s0891-5849(01)00521-4, PMID 11368926.
- 30. Petta TB, Nakajima S, Zlatanou A, Despras E, Couve-Privat S, Ishchenko A et al. Human DNA polymerase iota protects cells against oxidative stress. EMBO J. 2008;27(21):2883-95. doi: 10.1038/emboj.2008.210, PMID 18923427.
- 31. Shiga H, Heath EI, Rasmussen AA, Trock B, Johnston PG, Forastiere AA et al. Prognostic Value of p53, glutathione Stransferase {{pi}}, and thymidylate synthase for neoadjuvant cisplatin-based chemotherapy in head and neck cancer. Clin Cancer Res. 1999;5(12):4097-104. PMID 10632346.
- 32. Simons AL, Ahmad IM, Mattson DM, Dornfeld KJ, Spitz DR. 2-deoxy-D-glucose combined with cisplatin enhances cytotoxicity via metabolic oxidative stress in human head and neck cancer cells. Cancer Res. 2007;67(7):3364-70. doi: 10.1158/0008-5472.CAN-06-3717, PMID 17409446.
- 33. Townsend DM, Tew KD. The role of glutathione-S-transferase in anti-cancer drug resistance. Oncogene. 2003;22(47):7369-75. doi: 10.1038/sj.onc.1206940, PMID 14576844.
- 34. Toyokuni S, Okamoto K, Yodoi J, Hiai H. Persistent oxidative stress in cancer. FEBS Lett. 1995;358(1):1-3. doi: 10.1016/0014-5793(94)01368-b, PMID 7821417.
- 35. Trachootham D, Alexandre J, Huang P. Targeting cancer cells by ROS-mediated mechanisms: a radical therapeutic approach? Nat Rev Drug Discov. 2009;8(7):579-91*Jordan Journal of Biological Sciences. All rights reserved Volume 4, Number 3* 124. doi: 10.1038/nrd2803, PMID 19478820.
- 36. Bockmühl U, Schlüns K, Schmidt S, Matthias S, Petersen I. Chromosomal alterations during metastasis formation of head and neck squamous cell carcinoma. Genes Chromosomes Cancer. 2002;33(1):29-35. doi: 10.1002/gcc.1209.
- 37. Vojislav V, Trudey N, Hedley DW. Differential effects of buthionine sulphoximine in hypoxic and non-hypoxic regions of human cervical carcinoma xenografts. Radiother Oncol J Eur Soc Ther Rad Oncol. 2001;60(1):69-73.
- 38. Weydert CJ, Zhang Y, Sun W, Waugh TA, Teoh ML, Andringa KK et al. Increased oxidative stress created by adenoviral MnSOD or CuZnSOD plus BCNU (1,3-bis(2-chloroethyl)-1-nitrosourea) inhibits breast cancer cell growth. Free Radic Biol Med. 2008;44(5):856-67. doi: 10.1016/j.freeradbiomed.2007.11.009, PMID 18155673.
- 39. Williamson JM, Boettcher B, Meister A. Intracellular cysteine delivery system that protects against toxicity by promoting glutathione synthesis. Proc Natl Acad Sci U S A. 1982;79(20):6246-9. doi: 10.1073/pnas.79.20.6246, PMID 6959113.
- 40. Wiseman H, Halliwell B. Damage to DNA by reactive oxygen and nitrogen species: role in inflammatory disease and progression to cancer. Biochem J. 1996;313(1):17-29. doi: 10.1042/bj3130017, PMID 8546679.
- 41. Wu LL, Chiou CC, Chang PY, Wu JT. Urinary 8-OHdG: a marker of oxidative stress to DNA and a risk factor for cancer, atherosclerosis and diabetics. Clin Chim Acta. 2004;339(1-2):1-9. doi: 10.1016/j.cccn.2003.09.010, PMID 14687888.

42.

Yu NY, Brown JM. Depletion of glutathione $in\ vivo$ as a method of improving the therapeutic ratio of misonidazole and SR 2508. Int J Radiat Oncol Biol Phys. 1984;10(8):1265-9. doi: 10.1016/0360-3016(84)90330-4, PMID 6236185.