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several decades.


Powered by
RiboCeine™
RiboCeine™

RibCys

D-Ribose-L-Cysteine (DRLC)

Ribose-Cysteine

RiboCeine™

RiboCeine = RibCys = Ribose-Cysteine = DRLC
SUMMARY OF THE INVENTION

[0015] The present invention provides a method to treat a mammal threatened by, or afflicted with a hypoxic condition (hypoxia) comprising administering an effective amount of a compound of formula (Ia):

(RibCys) or a pharmaceutically acceptable salt thereof, effective to counteract the effects of said hypoxia in the tissue(s) of said mammal. Although depressed glutathione levels have been implicated in a number of hypoxic conditions, as discussed above, the use of RibCys or its salts to prevent, counteract or otherwise treat such conditions has
not been reported. It is believed that simply administering a GSH precursor such as cysteine will not be as effective in many instances of hypoxia, when the depletion of ATP stores contributes to inhibition to the biosynthesis of GSH. As well as functioning as a prodrug for cysteine, administration of effective amounts of RibCys can deliver amounts of ribose to ATP-depleted tissues that stimulate the in vivo synthesis of ATP and that also can stimulate the synthesis of NADPH (nicotinamide adenine dinucleotide phosphate, reduced). This coenzyme supplies the electrons to glutathione reductase, which in turn recycles oxidized GSH via GSSG, to free GSH, which resumes its protective role as a cofactor for antioxidant enzymes in the cell. Optionally, compound (Ia) can be administered with an additional amount of free ribose. Preferably, administration will be by oral administration, particularly in prophylactic or pre-loading situations, but parenteral administration, as by injection or infusion, may be necessary in some situations.
INDEPENDENT STUDIES ON RIBOCEINE™
Published Articles on RiboCeine™
(Rib-Cys, Ribose-Cysteine, D-Ribose-L-Cysteine)


30. Emokpae O, Ben-Azu B, Ajayi AM, Umukoro S. D-Ribose-L-cysteine attenuates lipopolysaccharide-induced memory deficits through inhibition of oxidative stress, release of


1. **RiboCeine Shown to Protect Against Oxidative Stress**


**Study Background**

Oxidative stress is a metabolic condition where excess free radicals are being produced. Chronic oxidative stress has been associated with many diseases and disorders including cardiovascular diseases, neurodegenerative disorders, cataract formation, inflammatory diseases, etc. Although there is no proven relationship that oxidative stress is the cause of these diseases, there is a significant body of evidence that oxidative stress (low glutathione levels) is prevalent in many disease states and disorders.

Basic science researchers in pursuit of determining whether certain compounds are effective in reducing oxidative stress require animal models to conduct their experiments. To mimic chronic oxidative stress in animals, an acute oxidative stress model is used to permit these experiments to be conducted in shorter time periods, thereby saving on time and cost. A widely accepted acute oxidative stress animal model is the acetaminophen over-dose model, wherein severe depletion of liver glutathione is manifested when toxic doses are administered.

Acetaminophen, a widely used pain killer, is not toxic at recommended doses, and is readily metabolized by the liver to non-toxic products, which are then excreted in the urine. However at high or toxic doses, the normal metabolic pathways become overwhelmed and the liver will, ironically, metabolize acetaminophen through a different pathway that produces a very reactive and toxic metabolite, thus triggering the development of acute oxidative stress. This toxic metabolite is detoxified by liver glutathione; however, once liver glutathione becomes depleted, this toxic metabolite
will react with liver cells leading to liver necrosis and eventually death of the animals.

To overcome acetaminophen-induced acute oxidative stress that causes severe depletion of liver glutathione, researchers administer test compounds believed to promote varying degrees of glutathione production. The compound’s effectiveness is determined by the level of protection it provides to the liver, and its ability to prevent animal death. Those compounds that exhibit the best protection to the liver and having the highest animal survival rates are deemed to be the superior compounds. The level of protection directly correlates with the compound’s ability to improve liver glutathione levels.

**Summary:** In this study, a total of 8 sulfhydryl-protected L-cysteine compounds, in addition to N-acetylcysteine (NAC) which is not sulfhydryl-protected, were evaluated in an *in vivo* mouse model to determine their ability to protect against liver toxicity from a high dose of acetaminophen. RiboCeine was among the sulfhydryl-protected compounds tested. In protecting the sulfhydryl (SH) group of L-cysteine, the authors used naturally-occurring endogenous substances to avoid any possibility of toxicity by the protecting substance itself.

**Part 1:** The experimental protocol involved the administration of a lethal dose (LD90) of acetaminophen where 90% of the mice were expected not to survive plus the test compounds. Toxicity was assessed on the basis of overall survival of the animals at 48 hours, as well as histological (cell pathology) criteria of liver cell damage assessed by an independent third party “who had no knowledge of the experimental protocols or sample identity”. RiboCeine was the only compound tested where no animal death occurred at 48 hours. All other compounds tested had varying rates of animal survival between 30% to 94%. The animals without intervention had only a 17% survival rate. RiboCeine “showed the best histological profile” with all animals showing a necrosis rating of +2 or below (range 4+ to 0). All other compounds tested had animals with histological ratings of 4+.

**Part 2:** In the *in vitro* study with cultured hepatocytes (liver cells), RiboCeine at 40% of the dose of NAC raised liver cell glutathione levels 130% better than NAC. Since BSO, an inhibitor of glutathione synthesis, prevented this glutathione increase, it was concluded that the L-cysteine from RiboCeine must have been utilized in the
newly formed glutathione.

**Conclusion:** The collective *in vivo* and *in vitro* data suggested that RiboCeine was readily bioavailable, was superior to the other compounds tested, and should serve as an effective cysteine delivery system to the liver.

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**RIBOCEINE WAS SHOWN TO BE 300% MORE EFFECTIVE THAN NAC IN RAISING LIVER GLUTATHIONE LEVELS**

On the table above, even though 2 ½ times more NAC was used in the incubation of these hepatocytes, the glutathione levels were 30% lower than the cells that were incubated with RiboCeine (RibCys). Therefore, RiboCeine was at least 300% more effective in raising liver cell glutathione than NAC was in this liver cell model.
2. Organ Glutathione Levels after RiboCeine


Study Background

It is well accepted by the scientific community that glutathione levels in cells are homeostatically controlled, and dramatic elevations in glutathione levels are not expected because its biosynthesis is stringently controlled by feedback inhibition\(^1\). Therefore, glutathione may only achieve a certain level before the biosynthetic machinery would be turned off, regardless of the level of amino acid precursors available in the cell\(^1\). However, in the presence of a toxic substance that requires glutathione for detoxification, the levels of glutathione in the liver are continually decreasing and virtually depleted in some cases (acetaminophen overdoses). The value of these glutathione elevation studies is not in the “absolute increase of glutathione achieved”, but rather the compound’s ability to maintain glutathione levels under oxidative stress conditions.

Glutathione levels in many organs fall as the result of fasting, and therefore, compounds can be tested in fasting animals for their ability to elevate and maintain organ glutathione.

Summary: In this study, RibCys (RiboCeine) was evaluated in fasting mice for its ability to improve glutathione levels in numerous organs at different time points after RiboCeine administration. After 8 to 10 hours of fasting, glutathione levels dropped approximately 43% in the liver, 41% in the bladder, 31% in the kidney, 25% in the heart and 60% in muscle. Other organs, such as the spleen, pancreas and lung, showed no significant differences in glutathione levels between the two nutritional states.
**Results:** “Glutathione in the liver was elevated 1.5 fold compared to untreated controls at the 16 hour time point. Kidney glutathione also was maximal at 16 hours and achieved 1.6 times control values. Glutathione in muscle achieved 2.5 times the levels in control animals, while the bladder was elevated 2.1 fold and the heart 1.8 fold.”

**Conclusion:** The authors concluded that “RibCys was able to maintain, and, in some organs, continued to elevate glutathione even though the animals were subject to continued fasting”. “The results from the present studies support the hypothesis that RibCys can serve as a reservoir for the crucial glutathione precursor, L-cysteine, and continually supply the amino acid as glutathione synthesis proceeds.”

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3. Inflammatory Bowel Disease and Glutathione


**Study Background**

Glutathione is the most important endogenous antioxidant for cellular defense against oxidative stress, and is vital for the integrity of the gut. Oxidant-mediated injury plays an important role in the pathophysiology of inflammatory bowel disease (IBD). Reactive oxygen species (ROS) have been implicated in the tissue destruction observed in IBD. These ROS include hydroxyl radical, superoxide radical, hydrogen peroxide and nitric oxide. ROS are extremely unstable because of their high reactivity, and can lead to lipid peroxidation and the oxidation of DNA and proteins.

**Summary:** Dextran sodium sulfate (DSS) induced colitis is a well-accepted model that produces colonic inflammation of the gut. This study compared the protective effects of three glutathione promoting agents that included RiboCeine. In this mouse model of colitis, these compounds were incorporated into the daily chow. The animals were provided with normal drinking water, but after three days, the water was supplemented with DSS. All animals remained on the assigned diets until they were euthanized on day 10. Mice administered DSS developed severe colitis and suffered weight loss.

**Results:** Colonic lesions significantly improved when RiboCeine was incorporated in the food (*P* < 0.001). Colon lengths of the colitis mice (DSS) were significantly decreased because of mucosal inflammation, edema and thickening (control 109±2.8 mm versus DSS 66±2.8 mm, *P*<0.001). In contrast, this decrease in colon length was significantly attenuated when treated with RiboCeine (84±4.2 mm, *P*<0.001) which is consistent with reduced inflammation of their colonic tissue. The mice receiving RiboCeine/chow had improved weight gains with no significant difference noted.
between normal control mice (control 29±0.9; DSS 26±1.0 grams) and RiboCeine (29±0.9 grams). Liver concentration of reduced glutathione, the major source of gut antioxidant, was depleted in colitis animals (DSS 4.81 +/− micromole/gram; control 6.53 +/− micromole/gram) and normalized with RiboCeine administration (P>0.05).

**Conclusion:** RiboCeine reduced disease activity in the mouse model of DSS induced colitis by restoring colonic glutathione, and may be a useful dietary supplement for the prevention or possible palliation of IBD in humans.
4. Antioxidant Therapy Prevents Age-Related Hearing Loss


Study Background

Age-related hearing loss (ARHL or presbycusis) refers to a gradual, progressive hearing loss that accompanies aging. The hearing loss is typically described as downward-sloping high frequency loss but may be associated with various types of system dysfunctions that progress with aging.

Age-related hearing loss is one of the most common conditions affecting the elderly population. Approximately 35 percent of adults age 65 and older have been reported to have some degree of age-related hearing loss. It is projected that by 2025, approximately 24.5 million Americans will be affected. Age-related hearing loss disables an individual's ability to communicate, thereby effectively jeopardizing their autonomy. Patients often experience associated depression and social withdrawal. Thus, age-related hearing loss presents a major public health concern.

Oxidative injury caused by free-radical damage is perhaps the most fundamental cause of age-related pathology in the biological aging of cells. Oxidative damage may be an important intrinsic factor in the pathogenesis of presbycusis. Increased concentrations of free radicals [(ROS) and reactive nitrogen species (RNS)] are implicated as a mediator of oxidative stress and damage to the inner ear in ARHL.

Summary: This study uses a strain of mice that progressively lose their hearing over their lifetime, and is a widely accepted model for the study of ARHL. A combination antioxidant cocktail which included RiboCeine, a critical precursor of cysteine for the biosynthesis of glutathione, was administered. The rationale for creating a
combination of antioxidant treatment was to target multiple sites within the oxidative pathway to retard or prevent oxidative stress.

Results: The data demonstrated that the administration of this combination of antioxidants to this animal model greatly attenuated the presentation of ARHL at all frequency levels compared to the control group.

Conclusion: The administration of combination antioxidants, which included RiboCeine, attenuated the presentation of AHRL, suggesting that such combinations might be useful in preventing or delaying ARHL, a major public health problem.
5. RiboCeine and Cardiovascular Health


**Overview:** Glutathione is a co-factor for glutathione peroxidase, the enzyme that catalyzes the detoxification of lipid peroxides. A low glutathione peroxidase activity and increased oxidized lipids are associated with cardiovascular disease.¹

**Methods:** Human lipoprotein(a) transgenic mice were treated with 4 mg/day ribose-cysteine (0.16 g/kg body weight) for 8 weeks. Livers and blood were harvested from treated and untreated controls (n = 9 per group) and glutathione concentrations, glutathione peroxidase activity, thiobarbituric acid reactive substances (TBARS), 8-isoprostanes and plasma lipid concentrations were measured.

**Results:** Ribose-cysteine increased glutathione concentrations in the liver and plasma (P < 0.05). Glutathione peroxidase activity was increased in both liver (1.7 fold, P < 0.01) and erythrocytes (3.5 fold, P < 0.05). TBARS concentrations in the liver, plasma and aortae were significantly reduced with ribose-cysteine (P < 0.01, P < 0.0005 and P < 0.01, respectively) as were the concentrations of 8-isoprostanes in the liver and aortae (P < 0.0005, P < 0.01, respectively). Ribose-cysteine treated mice showed significant decreases in Low Density Lipoproteins, human lipoprotein(a) and apoB concentrations (P < 0.05, P < 0.01 and P < 0.05, respectively), an effect which was associated with upregulation of the Low Density Lipoproteins receptor (LDLR).

**Conclusion:** As ribose-cysteine lowers Low Density Lipoproteins, human lipoprotein(a) and oxidized lipid concentrations, it might be an ideal intervention to increase protection against the development of atherosclerosis.

6. RiboCeine and Wound Healing


Overview: Wound healing and chronic wounds are serious public health issues. While wounds heal, cellular stores of antioxidants are depleted. D-ribose-L-cysteine is a precursor to the antioxidant glutathione. The effect of oral supplementation with D-ribose-L-cysteine on wound healing was studied in rats.

Methods: A rodent model of calibrated wounding was used. Group A rats were given D-ribose-L-cysteine for 1 week before wounding and for 3, 7, or 14 days after wounding. Group B rats were given D-ribose-L-cysteine only after wounding. Control animals were given no supplement. Photographic comparisons were made to study wound edema and inflammation. Wound strength was determined by using a laser-vacuum device.

Results: During healing, both Group A and B animals showed less edema and inflammation than Control. Group A animals had the weakest wounds at 3 days after surgery, but the strongest wounds after 14 days. Group B animals had similar wound strength to Control animals at 7 days, but stronger wounds after 14 days.

Conclusion: D-ribose-L-cysteine supplementation appears to reduce wound inflammation early after wounding and enhance wound strength by 14 days. This suggests that increased intracellular glutathione levels may improve and enhance wound healing.
7. **RiboCeine and Male Fertility**


**Overview:** This study investigated the effects of Ribose-cysteine on aluminum-induced testicular damage in male rats. There have been many studies that have been published on the toxic effects of aluminum on humans and animals. Over-exposure to aluminum has been shown to have damaging effects on testicular tissue affecting spermatogenesis (low sperm count, abnormal sperm morphology). Oxidative stress has been suggested as a cause for male reproductive testicular damage.

**Methods:** A total number of thirty-five (35) adult male Sprague-Dawley rats were divided into four groups (A-D). Group A (comprised five (5) rats) was designated the Control Group, received Physiological Saline; while groups B, C, and D (comprised ten (10) rats) were given 75 mg/kg, 150 mg/kg and 300 mg/kg of body weight of aluminum chloride respectively for 39 days. At day 40, the aluminum-treated groups were subdivided into sub-groups (B1, C1, D1) comprising of five (5) rats each, and received RiboCeine for twenty (20) days. Groups B, C and D remained on the normal dosage of aluminum chloride for three more weeks (59 days).

**Results:** There was a boost in fertility for all groups that received RiboCeine B1, C1 and D1, with improvement in all andrological parameters (sperm count, motility, morphology, and testosterone). These positive observations may be due to RiboCeine’s potent antioxidant properties.

**Conclusion:** RiboCeine treatment significantly attenuates aluminum-induced testicular toxicity in male Sprague-Dawley in rats.
8. Riboceine and Diabetes


Overview: Diabetes is the seventh leading cause of death in the US and a major cause of heart disease and stroke. Over 18% of pregnant women are affected by gestational diabetes. Insulin is generally the treatment of choice to control gestational diabetes, because it does not cross the placenta. However, this treatment requires daily injections and therefore oral hypoglycemic agents (OHAs) are also used, although the safety of these drugs in pregnancy, is not fully understood. The drug, streptozotocin is toxic to the insulin producing beta cells of the pancreas and will cause diabetes within 24 hours. Oxidative stress has been implicated to play an important role in diabetic complications. The purpose of this study is to determine the anti-diabetic potential of 4 OHAs and D-Ribose-L-Cysteine in comparison to insulin in pregnant streptozotocin-drug induced diabetic rats.

Methods: The study protocol included 40 pregnant female rats and had 8 study groups with 5 animals per group. Group A was the Negative Control – non-diabetic, Group B was the Positive Control – Diabetic; Group C received insulin; Group D received D-Ribose-L-Cysteine; Group E received Vildagliptin (OHA); Group F received Glibenclamide (OHA); Group G received Metformin (OHA) and Group H received Glipizide (OHA). Groups B-H received streptozotocin and developed diabetes within 24 hours.

Results: Blood glucose levels significantly decreased in all treatment groups compared to the diabetic control (p value < 0.0001). Insulin and D-Ribose-L-Cysteine had the greatest effect on blood glucose compared to the OHAs (p value < 0.0001). Malondialdehyde, a marker of oxidative stress (oxidation by-product of
polyunsaturated fats) was significantly decreased in the animals that received insulin, D-Ribose-L-Cysteine and OHAs (exception Group F) when compared to the diabetic positive control.

**Conclusion:** D-Ribose-L-Cysteine was similar to insulin in decreasing blood glucose levels in pregnant streptozotocin-drug induced diabetic rats. The OHAs were less effective. D-Ribose-L-Cysteine mitigates lipid peroxidation in this pregnant diabetic rat model as demonstrated by a decrease malondialdehyde levels. This study demonstrated that the potential benefits of D-Ribose-L-Cysteine as an effective OHA and could serve as a potent adjuvant in the management of diabetes in pregnancy. Further studies to determine the efficacy and safety in humans should be conducted.
9. RiboCeine and Alzheimer’s Disease


**Overview:** Oxidative stress-mediated cellular injury plays a crucial role in the pathophysiology of Alzheimer’s disease (AD), a progressive neurodegenerative disorder characterized by gradual deterioration in cognition and other behavioral phenotypes. The increase in lipid peroxidation and reduced endogenous antioxidant levels that occur in AD suggests oxidative stress contributes to the pathology of the disease. Lipid peroxidative tissue damage caused by free radicals triggers a vicious cycle of neuroinflammation that leads to progressive degeneration of the neuronal pathways responsible for learning and memory. Glutathione (GSH) is the most important intracellular antioxidant defense molecule in mammalian tissues, especially in the brain. This study seeks to evaluate the effects of D-Ribose-L Cysteine (DRLC) on memory deficits and the biochemical and histomorphological changes induced by lipopolysaccharide (LPS) in mice. Systemic administration of LPS causes a cluster of behavior derangements including memory decline through the induction of oxidative stress and neuroinflammation. The LPS-induced memory deficits closely reflects the pathologic changes seen in patients with AD and therefore this animal model can be used to detect compounds with cognitive-enhancing activities.

**Methods:** The study protocol included 60 male mice and had 6 study groups with 10 animals per group. Group 1 was the Control Group – Placebo; Group 2 was the negative control – AD; Group 3 received DRLC at 25mg/Kg; Group 4 received DRLC at 50mg/Kg; Group 5 received DRLC at 100mg/Kg and Group 6 received donepezil* (DPZ) at 1mg/Kg. Groups 2-6 received LPS to induce memory deficits (AD).

* FDA approved drug to treat dementia, aka Aricept®.
Results: DRLC reversed LPS-induced memory impairment and improved social recognition memory and interaction deficits. DRLC improved brain GSH, catalase and decreased malondialdehyde (marker for oxidative stress), and the inflammatory markers, tumor necrosis factor-alpha (TNF-alpha) and interleukin-6 (IL-6). There was also a decrease expression of nuclear transcription factor kappa-B (NF-kB). The involvement of NF-kB in neurodegenerative diseases such as AD, is well reported in the literature.

Conclusion: The results of this study suggest that DRLC has memory enhancing effects in mice treated with LPS, which induces memory deficits, through mechanisms related to the inhibition of oxidative stress, release of proinflammatory cytokines and expression of nuclear transcription factor kappa-B.

PPD 1/2020 sgn
INDEPENDENT STUDIES
1. RibCys – High LET Radiation (NTRS)

2. Effect of Ribose Cysteine Pretreatment


**Results**

- Ribose cysteine treatment reversed the acetaminophen-induced decline in hepatic non-protein sulfhydryl and renal GSH.
- Ribose cysteine treatment altered acetaminophen metabolite concentration in liver and kidney.
- Ribose cysteine does not inhibit acetaminophen activation in vitro.
- Since Buthionine sulfoximine pretreatment prevented the de novo biosynthesis of glutathione from RibCys, the mechanism by which RibCys protected against acetaminophen was by the synthesis of new glutathione.

*Acetaminophen = Tylenol*
3. GSH and Disease Progression

Summary

Changes in GSH levels and/or oxidation state have now been reported in nearly all major human diseases. Although in many cases these changes likely occur as a result of the underlying disease progression, in other cases these changes are closely linked to the onset and/or development of the disease. The growing recognition that GSH is involved in critical cell signaling pathways that are regulated by S-glutathionylation and/or the thiol redox status, and that GSH may function as a neurotransmitter or neuromodulator, provides considerable new insight into possible links between GSH and disease progression, and raises additional questions that can be addressed experimentally. In addition, the recognition that GSH is intimately involved in so many disease states has generated considerable interest in identifying therapies aimed at modulating GSH levels so as to modulate disease risk or progression. Although such therapies have significant hurdles to overcome, they offer significant promise for many human diseases.
4. Heavy Metals and Human Health


Review

Heavy Metals and Human Health: Mechanistic Insight into Toxicity and Counter Defense System of Antioxidants

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Abstract: Heavy metals, which have widespread environmental distribution and originate from natural and anthropogenic sources, are common environmental pollutants. In recent decades, their contamination has increased dramatically because of continuous discharge in sewage and untreated industrial effluents. Because they are non-degradable, they persist in the environment; accordingly, they have received a great deal of attention owing to their potential health and environmental risks. Although the toxic effects of metals depend on the forms and routes of exposure, interruptions of intracellular homeostasis include damage to lipids, proteins, enzymes and DNA via the production of free radicals. Following exposure to heavy metals, their metabolism and subsequent excretion from the body depends on the presence of antioxidants (glutathione, α-tocopherol, ascorbate, etc.) associated with the quenching of free radicals by suspending the activity of enzymes (catalase, peroxidase, and superoxide dismutase). Therefore, this review was written to provide a deep understanding of the mechanisms involved in eliciting their toxicity in order to highlight the necessity for development of strategies to decrease exposure to these metals, as well as to identify substances that contribute significantly to overcome their hazardous effects within the body of living organisms.

5. Conclusions

Agents responsible for multiple human complications vary grossly in their physicochemical properties, and metals are no exception. After entering an ecosystem, metals induce a broad range of physiological, biochemical, and behavioural dysfunctions via induction of oxidative stress in humans. Oxidative and nitritative stress developed in response to toxicants plays an important role in damaging biomolecules, as well as disrupting signalling pathways, which in turn leads to pathogenesis of multiple human diseases. Despite the protection afforded by the cellular redox environment in biological systems, its disruption due to exogenous stimuli or endogenous metabolic alteration leads to increased intracellular ROS/RNS levels. Buffering and muffling reactions between ROS/RNS generation and elimination to redress the deleterious effects caused by oxidative stress are maintained by complex antioxidant (enzymatic and non-enzymatic) systems. In terms of a reactivity standpoint, the enzymatic antioxidant system constitutes the first line of defence, followed by reduced thiols and low molecular weight antioxidants and then by a broad range of products from dietary sources. Defense systems for overcoming the deleterious effects of oxidative and nitritative stress generated by production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) are essential to maintenance of cellular homeostasis. However, depletion of the cellular antioxidant pool characterized by (a) increased ROS and RNS production; (b) depletion of free-radical scavengers (Vitamins E and C) and cellular antioxidants (largely GSH); and (c) inhibition of the activity of enzymes such as (GPx) glutathione peroxidase, GSH-reductase, GSH-transferase, catalase (CAT) and superoxide dismutase (SOD) that contribute significantly to the metabolism and detoxification of reactive oxygen species (ROS). Having grave consequences within the bodies of living organisms, maintaining the availability of essential and controlled distribution of toxic metal ions is an efficient means of protection against the deleterious effects of heavy metals. Accordingly, an improved understanding of the counter-productive and beneficial defensive mechanisms of dietary antioxidants support their role in therapeutics for metal induced oxidative stress. To bridge this knowledge gap, studies pertaining to elucidation of molecular mechanisms involved in imparting toxicity imposed by heavy metals are essential. In addition, detailed mechanistic studies underlying the beneficial effects of dietary antioxidants for their optimum dosage and duration of treatment will be helpful in the development of combinatorial strategies as part of effective treatment regimes for better clinical recovery in metal intoxication cases.
5. Free Radicals, Oxidative Stress, Antioxidants, Glutathione


Some internally generated sources of free radicals are[^8]

- Mitochondria
- Xanthine oxidase
- Peroxisomes
- Inflammation
- Phagocytosis
- Arachidonate pathways
• Exercise
• Ischemia/reperfusion injury

Some externally generated sources of free radicals are:
• Cigarette smoke
• Environmental pollutants
• Radiation
• Certain drugs, pesticides
• Industrial solvents
• Ozone


CONCEPT OF OXIDATIVE STRESS
The term is used to describe the condition of oxidative damage resulting when the critical balance between free radical generation and antioxidant defenses is unfavorable.[14] Oxidative stress, arising as a result of an imbalance between free radical production and antioxidant defenses, is associated with damage to a wide range of molecular species including lipids, proteins, and nucleic acids.[15] Short-term oxidative stress may occur in tissues injured by trauma, infection, heat injury, hypoxia, toxins, and excessive exercise. These injured tissues produce increased radical generating enzymes (e.g., xanthine oxidase, lipogenase, cyclooxygenase) activation of phagocytes, release of free iron, copper ions, or a disruption of the electron transport chains of oxidative phosphorylation, producing excess ROS. The initiation, promotion, and progression of cancer, as well as the side-effects of radiation and chemotherapy, have been linked to the imbalance between ROS and the antioxidant defense system. ROS have been implicated in the induction and complications of diabetes mellitus, age-related eye disease, and neurodegenerative diseases such as Parkinson's disease.[16]

Oxidative stress and human diseases
Cardiovascular diseases
Carcinogenesis
Free radical and aging
Oxidative damage to protein
Lipid peroxidation
Oxidative damage to DNA

ANTIOXIDANTS

Glutathione


CONCLUSION

Free radicals damage contribute to the etiology of many chronic health problems such as cardiovascular and inflammatory disease, cataract, and cancer. Antioxidants prevent free radical induced tissue damage by preventing the formation of radicals, scavenging them, or by promoting their decomposition. Synthetic antioxidants are recently reported to be dangerous to human health. Thus the search for effective, nontoxic natural compounds with antioxidative activity has been intensified in recent years. In addition to endogenous antioxidant defense systems, consumption of dietary and plant-derived antioxidants appears to be a suitable alternative. Dietary and other components of plants form a major source of antioxidants. The traditional Indian diet, spices, and medicinal plants are rich sources of natural antioxidants; higher intake of foods with functional attributes including high level of antioxidants in antioxidants in functional foods is one strategy that is gaining importance.

Newer approaches utilizing collaborative research and modern technology in combination with established traditional health principles will yield dividends in near future in improving health, especially among people who do not have access to the use of costlier western systems of medicine.
6. Glutathione S-transferase T1-1 (GSTT1-1) Is Lacking in 80% of Asians


Abstract
Glutathione S-transferases (GSTs) are an important part of the cellular detoxification system and, perhaps, evolved to protect cells against reactive oxygen metabolites. Theta is considered the most ancient among the GSTs and theta-like GSTs are found in mammals, fish, insects, plants, unicellular algae, and bacteria. It is thought that an ancestral theta-gene underwent an early duplication before the divergence of fungi and animals and further duplications generated the variety of the other classes of GSTs (alpha, mu, phi, etc.). The comparison of the aminoacidic homologies among mammals suggests that a duplication of an ancient GST theta occurred before the speciation of mammals and resulted in the subunits GSTT1 and GSTT2. The ancestral GST theta has a dehalogenase activity towards several halogenated compounds, such as the dichloromethane. In fact, some aerobic and anaerobic methylotrophic bacteria can use these molecules as the sole carbon and energy source. The mammalian GST theta cannot sustain the growth of bacteria but still retains the dehalogenating activity. Therefore, although mammalian GST theta behaves as a scavenger towards electrophiles, such as epoxides, it acts also as metabolic activator for halogenated compounds, producing a variety of intermediates potentially dangerous for DNA and cells. For example, mice exposed to dichloromethane show a dose-dependent incidence
of cancer via the GSTT1-1 pathway. Because GSTT1-1 is polymorphic in humans, with about 20% of Caucasians and 80% of Asians lacking the enzyme, the relationship between the phenotype and the incidence of cancer has been investigated extensively in order to detect GSTT1-1-associated differential susceptibility towards endogenous or exogenous carcinogens. The lack of the enzyme is related to a slightly increased risk of cancer of the bladder, gastro-intestinal tract, and for tobacco-related tumors (lung or oral cavity). More pronounced risks were found in males with the GSTT1-null genotype for brain diseases and skin basal cell carcinomas not related to sunlight exposures. Moreover, there was an increased risk of kidney and liver tumors in humans with the GSTT1-1 positive genotype following exposures to halogenated solvents. Interestingly, the liver and kidney are two organs that express the highest level of GST theta in the human body. Thus, the GSTT1-1 genotype is suspected to confer decreased or increased risk of cancer in relation to the source of exposure; in vitro studies, mostly conducted on metabolites of butadiene, confirm the protective action of GSTT1-1, whereas, thus far, experimental studies prove that the increasing risk is limited.
RESEARCH STUDIES COMPARING GLUTATHIONE TO OTHER ANTIOXIDANTS

Research Studies on Pubmed.gov
April 18, 2016 compared to August 22, 2020

* Pubmed.gov is the online medical science library of the U.S. Government.

† ALA (Alpha-Lipoic Acid)
In the past several months I have been working with Chinese associates in various Max markets. In many of my phone conversations I have received many questions relating to the Max products and in particular RiboCeine™. To assist these associates and others I have compiled a listing and summary of studies that involved RiboCeine and have been published in scientific journals. I have provided the scientific abstract from PubMed.gov as well as a summary of the conclusions. I sincerely thank Dr. Scott Nagasawa for his encouragement, his guidance and his assistance. I hope this booklet is of help to all the Max Associates. As new material becomes available I will attempt to add to meaningful summaries.

Jennifer Tsai
April 2016

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**Updated 2020**

Science doesn’t stand still and research is an ongoing effort. The study of GLUTATHIONE is also a work in motion! The health community focusing on GLUTATHIONE, has taken an interest in the Max patented and proprietary ingredient RiboCeine™. Since we first prepared the summary of independent studies in 2016 there have been an additional 10 independent research studies published in scientific journals and the studies are now listed in the United States research library at PubMed.gov. I hope you enjoy reading them and learn more about the importance of GLUTATHIONE to good health and the POWER OF RIBOCEINE. Again, I want to thank Dr. Scott Nagasawa for his encouragement and his assistance in bringing this information to you.

Jennifer Tsai
August 2020