Glutathione related disorders: do seaweeds have potential for cure?

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ABSTRACT :

Research on glutathione metabolism has largerly contributed to the advancement of varied disciplines of science over the past century. This ubiquitous wonder molecule distributed in plants animals and microbes has a plethora of functions essential for antioxidant defense, redox balance and cellular regulation to name a few. Dysregulation of glutathione homeostasis and metabolism results in a number of human diseases, including cancer, ageing related disorders, inflammatory, neurodegenerative, metabolic as well as liver diseases. Numerous therapeutic drugs have shown adverse health effects. Amidst the chaos a natural source of Glutathione may be regarded as a ray of hope towards successful management of glutathione related disorders. Seaweeds are rich in bioactive compounds which have important pharmaceutical and biomedical values. Seaweeds specifically grow in inter-tidal zones and deep sea coast lines and are thus exposed to constant variation in their habitat in terms of changing oxygen level due to tides, season, temperature, photoperiod and salinity. Thus they are better adapted to environmental stress which is one of the factors leading to oxidative stress and thus presumed to have better antioxidative defense. While humans have taken limited advantage of natural populations of seaweeds for centuries, it is in recent years that we have come to realize the potential of seaweeds. Seaweeds have the potential to produce a vast array of products ranging from foodstuffs, industrial chemicals to compounds with therapeutic and bioremediation activity virtually from a untapped source. They are also reported to have natural assemblages of glutathione. Thus, the demand of the day is to extract the naturally occurring glutathione and formulate it as a drug (keeping in view its low bioavailability and transient cellular transport) which would act as a promising cure for a variety of disorders.

Keywords: Glutathione, oxidative stress, seaweeds, phenols, flavonoids.

INTRODUCTION:

Research on Glutathione (GSH) (γ-glutamyl-cysteinly-glycine) synthesis, regulation and regeneration has immensely contributed to the advancement of nutritional, biochemical and pharmacological sciences over the past century. It is a major low molecular weight thiol approaching millimolar concentrations in various tissues. It is a potent antioxidant, redox and cell signaling (cell cycle regulation, proliferation and apoptosis) regulator synthesized *de novo* in mammalian cells that defends against toxicant insults. It is ubiquitous in plants, animals and microorganism with a multitude of functions [1- 3].

GSH synthesis is a two-step ATP consuming enzymatic process involving the formation of γ-glutamyl-cysteine by γ-glutamyl-cysteine ligase (GCL) and addition of glycine to the previously formed di-peptide by glutathione synthase (GS). The activity of GCL is a major determinant of the rate of GSH synthesis. The activities of enzymes involved in GSH synthesis are controlled at transcriptional, translational and post translational levels. Although it is synthesized and metabolized intracellularly, its catabolism occurs extracellularly by a series of enzymatic reactions and plasma membrane transport steps [4]. The compartmentalization of cytosolic GSH into nucleus, mitochondria and endoplasmic reticulum includes varied redox pools that are distinct from cytoplasmic pool in terms of their redox potential and their control of cellular activities [5]. Within the nucleus it maintains protein sulfydryl groups for DNA repair and expression and acts as a hydrogen donor for reduction of ribonucleotides to deoxy ribonucleotides [6]. Within the endoplasmic reticulum it predominantly occurs in its oxidized form (GSSG) and favours disulfide bond formation and folding of nassent proteins [7]. Inside the mitochondria it occurs mostly in its reduced form and holds a minor share of the entire GSH pool. The major redox buffering systems within the mitochondria are the GSH, GRx (glutaredoxin) and TRx (thioredoxin) system which coordinatedly protect it against the generation of oxidant species owing to cellular repiration [8]. Four major

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classes of GSH dependant enzymes contribute to cellular redox homeostatis: Glutathione peroxidases (GPx), glutathione transferases (GST), glutathione reductases (GR) and glutaredoxins.

GSH plays a vital role in detoxification of a variety of electrophillic compounds, peroxides and xenobiotics, via thiol disulfide exchange reactions, signal transduction pathways, cytokine production, immune response regulation and protein glutathionylation. It also acts as a key cellular regulator and plays an important role in many metabolic pathways. Some of the major functions of glutathione are listed in the table below.

Table 1: Major functions of glutathione. [9-15]

	FUNTION	MECHANISM
1	Antioxidant defence	• Reactive Oxygen Species (ROS) and Free radical scavenger • Removal of Lipid peroxides and hydrogen peroxides • Inhibits oxidation of Bio molecules
2.	Cellular regulator	• Sustainment of intracellular redox balance • Protein sysnthesis modulation (protein s-glutathionylation). • DNA synthesis modulation by maintaining reduced Glutaredoxin or thioredoxin . • Modulate activity of neurotransmitter receptors. • Effect in cellular proliferation, differentiation and apoptosis • Role in cytokine synthesis and immune response • Maintenance of functional and structural integrity of mitochondria
3	Metabolism	• Prostaglandin and leukotrines production • Formation of formate from formal dehyde • Synthesis of D lactate from methylglyoxal • Production of mercapturates from electrophiles • Production of glutathione nitric oxide adducts and thus nitric oxide homeostasis. • Accumulation and transference of cysteine.

GLUATHIONE DEFICIENCY AND DISEASES

Perturbations in GSH homeostasis and metabolism are implicated in the etiology and progression of a number of human diseases, including cancer, diseases of aging, cystic fibrosis, adult respiratory distress syndrome, and cardiovascular, inflammatory, immune, metabolic, liver and neurodegenerative diseases [16]. Owing to the pleiotropic effects of GSH on cell functions, it has been quite difficult to define the role of GSH in the onset or the expression of human diseases. GSH levels and its metabolism can be compromised by inherited or acquired defects in the enzymes, transporters, signaling molecules, or transcription factors that are involved in its homeostasis, or from exposure to reactive chemicals/ metabolic intermediates. GSH deficiency or a decrease in the GSH/GSSG ratio manifests itself largely through an increased susceptibility to oxidative stress, and the resulting damage is thought to be involved in diseases, such as cancer, Parkinson's disease, and Alzheimer's disease. Also, alterations in GSH levels hamper immune system function, and are thought to contribute in the aging process. Certain hereditary deffects are also been observed in patients with inborn errors of GSH metabolism. Out of the 6 enzymes of γ - glutamyl cycle, several diseases have been associated with 5 of these enzymes excepting γ- glutamyl cyclotransferase [17, 18]. These hereditary diseases manifest as haemolytic anemia, neurological defects like spino-cerebellar degeneration, peripheral neuropathy, myopathy and CNS disorders, amino aciduria and metabolic acidosis [17, 18]. Several animal studies with these enzyme deficiencies showed growth failure, shortened life span, cataracts, lethargy, defective gastrulation and infertility. Continous supplementation of the enzymes to these animals showed improvement in disease conditions, restored fertility and even extended the life span [19, 20]. The higher GSH levels in some tumor cells are also typically associated with higher levels of GSH-related enzymes and transporters. Although neither the mechanism nor the implications of these changes are well defined, the high GSH content makes cancer cells chemoresistant, which is a major factor that limits drug treatment. The following section deals with the relationship between imbalances in GSH homeostasis and pathogenesis of several human diseases.

Apoptosis: Apoptosis is a highly organized pathway of cell death in which cells activate enzymes that degrades the cells own nuclear DNA and nucleo cytoplasmic proteins. Initial stages of apoptosis are characterized by Reactive Species (RS) formation, changes in intracellular ionic homeostasis, cell shrinkage, loss of membrane lipid asymmetry and chromatin condensation. Later stages associated with the execution phase of apoptosis are characterized by activation of execution caspases and endonucleases, apoptotic body formation and cell fragmentation [21, 22]. Intracellular GSH loss is an early hallmark in the progression of cell death in response to different apoptotic stimuli. Several studies have shown a correlation between GSH depletion and the progression of apoptosis. [23, 24] Apoptosis induced by death receptor activation or cytokine withdrawal has been shown to induce GSH loss by the activation of a plasma membrane efflux transport for GSH and not by its oxidation to GSSG. The resulted GSSG and/or GSH-conjugates generated are toxic to the cell and must be removed by efflux pumps. This further depletes intracellular GSH pools

by the impairment of GSSG recycling to GSH through the action of the GR and NADPH. Finally, GSH depletion and RS formation might regulate the induction of apoptosis or cytotoxicity by RS-mediated signaling (through ROS or RNS), thiol-exchange reactions or protein oxidation-modifications (S-glutathionylation, S-nitrosylation), or GSH conjugation (by the action of GST).

Cancer: Glutathione has been shown to regulate the prevention as well as progression of carcinogenesis in different ways. The protective effect is mediated either by its antioxidant role or by GST-mediated phase II detoxification reactions that detoxifies the carcinogens produced by UV exposure, chemical agents, environment, inflammation and diet. However, transformed cells have shown to have increased levels of expression for several GSH enzymes. The increase in cell GSH is a major contributing factor to drug resistance by binding to or reacting with drugs, preventing damage to proteins or DNA, or by participating in DNA repair processes [25]. A more reduced intracellular environment encourages proliferation and reduced apoptosis of tumour cells by affecting caspases and transcription factor activation, ceramide production , thiol redox signaling and phosphatidylserine externalization [26, 27]. Therapeutic strategies based on GSH depletion (by use of L- buthionine sulfox imine, the inhibitor of GCL, as an adjuvant chemotherapeutic agent and stimulation of GSH efflux pumps) have shown to sensitize cells to effects of chemotherapy [28, 29].

Ageing: GSH level falls in all tissues with age, due to a corresponding fall in GCL and GS gene expression [30, 31]. Age-dependent fall in GSH may contribute to many of the age-associated diseases. How aging affects the expression of GCL and GS at the molecular level remains largely unclear.

Diabetes mellitus: Insulin deficiency lowers the expression of GCL and reduces GSH content in erythrocytes and blood plasma of diabetic patients. Changes in GSH dependent enzyme activities, such as glutathione peroxidase, gama glutamyl transpeptidase and glutathione S tranferase are also noted in diabetes [32, 33, 34]. High glucose by itself was also shown to reduce GCLC transcription in mouse endothelial cells [35]. Decreased GCLC expression due to hyperglycemia and insulin deficiency can lead to decreased GSH levels that impair antioxidant defense.

Neurodegenrative disorders: Diseases linked to in born errors in GSH metabolism has been reported to manifest central nervous system (CNS) dysfunctions. Although small, the brain uses about 20% of the body's oxygen supply and a considerable amount is converted to ROS. GSH may act as a neuromodulator for CNS activities against oxidative stress. Astrocytes are the major contributors of GSH in the brain. Consistent with a neuroprotective role, reduced GSH levels are reported in cases of various neurodegenerative disorders. GSH content is significantly lower in the substantia nigra of Parkinsons disease patients [36]. Recent clinical study using NMR spectroscopy showed reduced GSH levels in the brain tissues of Alzheimer's disease and multiple sclerosis patients compared to healthy subjects [37, 38]. The vital role played by GSH in neuronal survival is suggestive towards development of therapies aimed at restoring GSH levels in brain [39].

HIV: Low levels of GSH in blood plasma, epithelial linning fluid, peripheral blood mononuclear cells and monocytes, are observed in HIV infected individuals and is associated with lower rates of survival of affected patients [40]. Lower GSH levels favors the viral replication in HIV by enhancing signal transduction pathways (activates NFκB) associated with HIV expression and facilitate disease progression [41]. Moreover $CD4^+$ lymphocyte depletion follows HIV progression and decreases in GSH levels contributes to apoptosis in these $CD4^+$ lymphocytes. There is an intricate balance between GSH levels and cell signaling pathways involved in host immune system response.

Liver diseases: Liver holds a major share of GSH. Hepatic intracellular GSH levels in the range of 5-10 mM. Owing to the high intracellular GSH content it acts as a major detoxifying organ of the body. The alterations in the level of GSH contribute to several major liver dysfunctions and in some cases it can be conditionally lethal. Conditions causing defective intracellular transport or depletion in GSH level can lead to several liver dsyfunctions like, Chronic viral hepatitis, alcoholic liver diseases, drug induced liver injury, non- alcoholic fatty liver diseases and even hepatocellular carcinoma. In alcoholic liver diseases alcohol causes inactivation of mitochondrial transport of GSH, so decrease in mitochondrial GSH mediates ROS dependent cell death, which in turn contributes to the progression of hepatic fibrosis leading to cirrhosis. [42] In Chronic hepatitis C, several evidences had confirmed the cellular damage to be because of increased ROS production and are associated with decreased GSH levels in hepatic and plasma fractions and also in peripheral blood mono nuclear cells. [43] The most common liver disease worldwide is Non Alcoholic Fatty Liver Disease (NAFLD) in which the role of inflammation and oxidative stress may be confirmed by the "two –hit" theory of Day et al. 98 [44], according to which triglycerides and free fatty acid accumulation as well as lipid peroxidation related mitochondrial dysfunction and inflammation results in hepatocyte damage and development of liver fibrosis. However, the traditional 'two-hit' pathophysiological theory has been challenged as knowledge of the interplay between insulin resistance, adipokines, adipose tissue inflammation and other less recognised pathogenetic factors have increased over the last few years. Recently this two hit theory have been replaced by "multi- hit "theory whereby it has been suggested that hepatic steatosis may represent an epiphenomenon of several distinct injurious mechanisms [45] .Drug induced liver injury, mostly acetaminophen cause's liver cell damage by decrease in liver GSH levels. The selective depletion of GSH in mitochondria can sensitize hepatocytes to the oxidative effects of cytokines such as TNF α, IL1β, transcription factors like NFκB and AP-1, which regulates Matrix metalloproteinase 1. All of these increase oxidative stress with generation of ROS, which consequently increases apoptosis and finally causes carcinogenesis like Hepatocellular carcinoma. Cer-

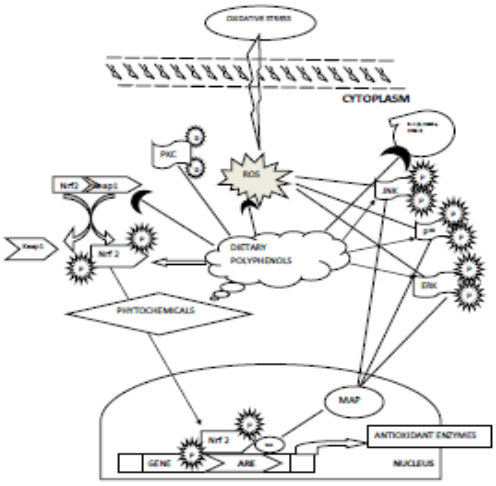
tain therapeutic drugs have shown hepatotoxic effect. Most of the Drug Induced Liver Injury (DILI) do not occur in a predictable dose dependent manner, which is the primary cause of its delayed recognition. Out of the several factors leading to DILI, reactive metabolite formation, ROS, depletion of antioxidant and interference of mitochondrial respiration plays a major role. The ROS generated in DILI, may be due to cytosolic stress during drug metabolism and / or subsequent response by injured liver cell. The typical example of DILI is that of Acetoaminophen(APAP) . The ROS produced by these drugs generates N-acetyl-p-quinoneimine (NAPQ1) by Cyt P450. NAPQ1 shows oxidative capacity through covalent modification of protein as well as reduction of GSH/GSSG ratio. APAP also causes hepatotoxicity by production of ROS, RNS and peroxidation reaction products. Drug toxicity can also induce inflammatory response through production of cytokines such as TNF α, IL6, IL1β and IL1α and IFN $^{\gamma}$. There are many studies reporting role of N-acetyl-cysteine (NAC), the precursor molecule for GSH synthesis in APAP induced liver injury.NAC significantly reduces the level of hepatic TNF α, IL6 in rat liver. Another drug cyclosporine A, an immuno suppressive agent exert hepatotoxic effect by stimulation of ROS formation and depletion of hepatic anti oxidant defence. There is a decreased hepatic level of nitric oxide (NO) and malonyl aldehyde (MDA) and increased superoxide dismutase (SOD) activity. It increases the membrane lipid peroxidation causing cell death. NAC treatment protects against the toxicity caused by Cyclosporine A through its antioxidant and radical scavenging action [46].

PHYTOCHEMICALS AS ANTIOXIDANTS

Plants synthesize a multitude of compounds, most of which are physiologically active upon consumption. Many of them are highly beneficial to health; many others are toxic. Plant foods provide an energy source that drives the metabolic process; the amino nitrogen that is the raw material for protein and nucleic acids synthesis; the essential fatty acids that form the cytomembranes and eicosanoids/docosanoids; the vitamins that function as coenzymes, metabolic regulators, and antioxidants; and minerals. Furthermore, there are additional arrays of compounds in plants, called secondary plant products or phytochemicals ("phyto" means plant). The term phytochemicals refers to a variety of non nutritional biologically active compounds in plant foods that confer various health benefits beyond basic nutrition. The major classes of phytochemicals include: alkaloids, flavonoids, glycosides, phenolics, saponins, tannins, terpenes, anthraquinones, essential oils and steroids [47]. Their nutritional functions had been overlooked until recently, when their protective effects against some diseases were investigated. Polyphenols in food plants are a versatile group of phytochemicals with many potentially beneficial activities in terms of disease prevention. In vitro cell culture experiments have shown that polyphenols possess antioxidant properties, and it is thought that these activities account for disease-preventing effects of diets high in polyphenols. Sulforaphane, Curcumin, Epigallocatechin gallate (EGCG), Allyl sulfide, Resveratrol, Capsaicin, (10)-shogaol, Lycopene, Carnosol, Cinnamaldehyde, Xanthohumol, Nordihydroguaiaretic acid (NDGA), Hydroxytyrosol and Quercetin are a few documented polyphenols with well pronounced antioxidant defence properties [48]. However, polyphenols may be regarded as xenobiotics by animal cells and are to some extent treated as such, ie, they interact with phase I and phase II enzyme systems. Dietary plant polyphenols, namely, the flavonoids, modulate expression of an important enzyme in both cellular antioxidant defenses and detoxification of xenobiotics, ie,_gamma - glutamylcysteine synthetase, the rate limiting enzyme in the synthesis of the glutathione. In vitro and in vivo experiments showed that flavonoids increase expression of gamma-glutamylcysteine synthetase with a concomitant increase in the intracellular glutathione concentration. As glutathione contributes towards redox regulation of transcription factors and enzymes for signal transduction, polyphenol mediated regulation of glutathione, altering cellular processes is seemingly evident. Glutathione is important in many diseases, and regulation of intracellular glutathione concentrations may be one mechanism by which diet influences disease development [49].

Mechanism of action of dietary polyphenols: One of the important system through which dietary polyphenols mediate their antioxidant activity is through the Nrf2 (nuclear factor erythroid 2 [NF-E2]-related factor 2 [Nrf2])–Keap1 (Kelch-like erythroid cell-derived protein with CNC homology [ECH]-associated protein 1 system. The transcription factor, Nrf2 works in collaboration with the adapter protein Keap1. In normal cellular conditions the binding of Nrf2 to keap 1 promotes ubiquitination of Nrf2 followed by proteosomal degradation. Under stress conditions several protein kinases disrupt this association and direct migration of Nrf2 into the nucleus, where it binds to the Antioxidant Response Elements (ARE) with the help of small regulatory proteins and leads to enhanced synthesis of antioxidant enzymes. Dietary polyphenols induces Nrf2-ARE binding by activation of kinases (JNK, ERK, P ^{38}), phosphorylating Nrf2 to disrupt Keap1 binding and thus enhances the cells defence against toxicant/stress [50]. (Figure 1)

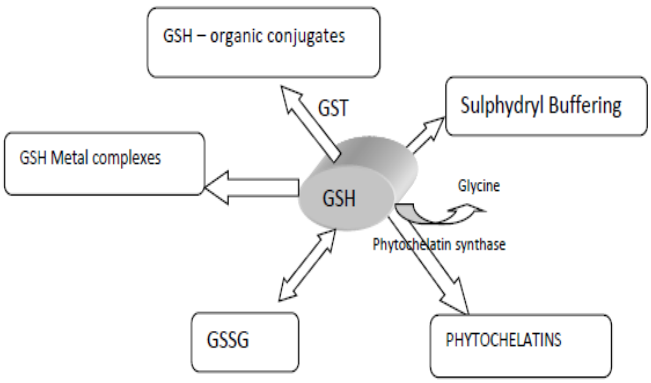
Figure 1: **Role of dietary polyphenols [48].**



SEAWEEDS AS SOURCE OF POLYPHENOLS AND GLUTATHIONE:

Seaweeds (marine macro-algae) are one of the important components of coastal marine ecosystem. They are principally of three types based on colour of their thallus, (i.e red- Rhodophyta, brown - Phaeophyta and green – Chlorophyta). Macro algae account for an estimated 5% of the total marine primary production. Seaweeds are rich in polysaccharides, vitamins, minerals and trace elements [51] for which the consumption of marine algae has been increased globally [52], especially by the vegetarians [53]. Though the research in the field of enumeration of glutathione presence in seaweed has not yet been extensive, still there are a few reports to substantiate. The occurrence of metal complexing thiol peptides, polychelatins and glutathione was found in natural assemblages of seaweed. The red, brown and green seaweeds were estimated for the presence of GSH [54]. Numerous in vivo and in vitro studies of dietary seaweed report increased apoptosis of tumor cell, inhibition of tumor cell adhesion and enhanced immune responses [55]. When seaweeds are subjected to a mixture of metals, GSH may be used to combat oxidative stress for production of phytochelatins and/or to comlex certain metals [54]. Evidence of distribution of free L-cysteine and glutathione in 37 species of algae including 9 chlorphyta, 16 phaeophyta and 12 rhodophyta were carried out by Kakinuma M et al, 2001 [56]. It has been reported that GSH functions as a storage pool of excess cysteine and that cysteine can be supplied by degradation of GSH during sulfur starvation in algae [57]. Intracellular glutathione concentrations in macro algae are not significantly altered by long term exposure to heavy metals. Glutathione levels are tightly regulated, despite substantial Polychelatin synthesis, which is consistent with the cell's need to maintain glutathione for other essential functions. [58]. These finding provide a hope for utilizing naturally available storehouse (seaweeds) of Glutathione in modulation of GSH in patients / individuals with related disorders of glutathione metabolism.

Figure 2: Schematic representation of functions of GSH in a eukaryotic algal cell.



GLUTATHIONE SUPPLEMENTATION.

Supplementation with glutathione has been met with little success as the bioavailabilty of glutathione is low due to its short lived transport through the cellular network [59]. Dietary repletion of systemic GSH plays an important role in the management of conditions as diverse as Alzheimer's disease, atherosclerotic vascular degeneration, cataract, lung insufficiencies, Parkinson's disease, and many others [60]. Liposomal glutathione supplementation restores TH1 cytokine response to M. Tuberculosis infection in HIV affected patients. 13 weeks of liposomal GSH supplementation increased TH1 cytokines, IL-1β, IL-1$^{\gamma}$, IFN-$^{\gamma}$ & TNFα and also led to substantial decrease in levels of free radicals and immunosuppressive cytokines, IL-10 and TGF-β relative to the control group [61]. Hepatic methionine adenosyl transferase (MAT) catalyses the formation of S–adenosyl Methionine, whose perturbations are usually linked to hepatic disorders. MAT transforms methionine into cysteine which is a limiting factor for GSH synthesis. MAT is low in immature infants and Parenteral Nutrition (PN) individuals. Prevention of peroxides generation (because of low GSH) in PN/ correction of redox potential by adding GSH in PN are not sufficient even if to same extent it lowers the degree of hepatic disorders. As the effectiveness of oral supplementation with GSH has been controversial, the effects of a novel sublingual form of GSH on oxidative stress markers (liver function markers, vitamin E, lipid status, reduced thiols) was studied. The sub lingual route allows to bypass the hepatic first pass metabolism [62]. So, compared to oral GSH group, an increase of total and reduced GSH was observed in sublingual GSH group and no adverse reports were obtained for hepatic status and lipid status markers as well, suggestive of the significant superiority of the sub lingual form over oral GSH [63]. Therapeutic possibilities of N-acetyl cysteine (NAC) in hepatic disorders have been extensively reviewed and several positive outcomes have been reported concerning animal models. NAC was reported to increase GSH levels in hepatic cells, having in turn antioxidant effects in cells. NAC also stimulates the activity of cytosolic enzymes, such as Glutathione reductase [64]. Dietary supplementation with GSH precursor amino acids can restore GSH synthesis and lower oxidative stress and oxidant damage in the face of persistent hyperglycemia in type 2 diabetic patients [65]. Studies with NAC have shown promising results in mouse models of Alzhimers and Parkinsons disease [66]. Effectiveness of intramuscular GSH administration to murine models of induced HIV showed reduced proviral load in the first phase of infection [67].

PERSPECTIVES

GSH has wide applications as far bio medical and pharmaceutical aspects of diseases are concerened. Due to its involvement in central regulatory and metabolic pathways of our body, the modulation of it can play a major role in combating disease conditions. Seaweeds are a potential reserve of naturally occurring antioxidants and have been used since times immemorial in diets and formulations in many parts of the world. The only drawback being the adverse effects of phytochelatins in concentrating metals. If the active principles from seaweeds can be extracted and formulated to serve as a source of GSH, it would overrule the adverse effects of metal chelation and can play an im-

portant role in regulating GSH levels in pathological conditions. Yet another scope for preparation of a formulation of theses active principles which could escape the gut lining/ assimilatory pathway would hold enormous possibilities towards increased uptake of oral glutathione and thereby help medical science explore new possibilities towards treating glutathione related disorders.

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