IJPSR (2014), Vol. 5, Issue 3 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 01 October, 2013; received in revised form, 21 November, 2013; accepted, 16 February, 2014; published 01 March, 2014

CLINICAL EVIDENCES OF OXIDATIVE STRESS AS A BIOMARKER IN VARIOUS TYPES OF CANCERS: A REVIEW

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Keywords:

Cancer, Oxidative stress, Free radicals, Antioxidant, Lipid peroxidation

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ABSTRACT: Free radicals play an effective role in the pathogenesis of different pathological diseases together with cancer. Potential biological targets for free radical attack comprise lipids, proteins and nucleic acids. Free radical induced lipid peroxidation causes a loss of cell homeostasis by modifying the structure and functions of cell membrane. The most important characteristic of lipid peroxidation is to cause a substantial DNA- MDA (Malondialdehyde) adducts by interacting with cellular DNA. Enzymatic antioxidants Superoxide dismutase (SOD), Catalase (CAT), Glutathione peroxidase (GPx) and non-enzymatic antioxidants vitamin E, Reduced glutathione (GSH) proceed synergistically with one another to detoxify the effects of lipid peroxidation. There is occurrence and contribution of oxidative stress in different types of cancer including, Ovarian cancer, Breast cancer, Oral cancer, Lung cancer, Leukemia, Cervical cancer, Prostate cancer, Gastric and Colon cancer which increase the pathogenesis and cause tissue damage in cancer. Lipid peroxidation and levels of enzymatic and non-enzymatic antioxidants can be used as markers of oxidative stress in various cancers.

INTRODUCTION: Oxidative stress is caused due to a disturbance in the balance between the production of reactive oxygen species (ROS) and efficiency of the antioxidant defense.

In other words, oxidative stress results if excessive production of ROS completely defeats the antioxidant defense system or if there is a significant decrease or lack of antioxidant defense [1]. Potential biological targets for free radical attack include lipids, proteins and nucleic acids [2].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.5(3).657-65

Article can be accessed online on: www.ijpsr.com

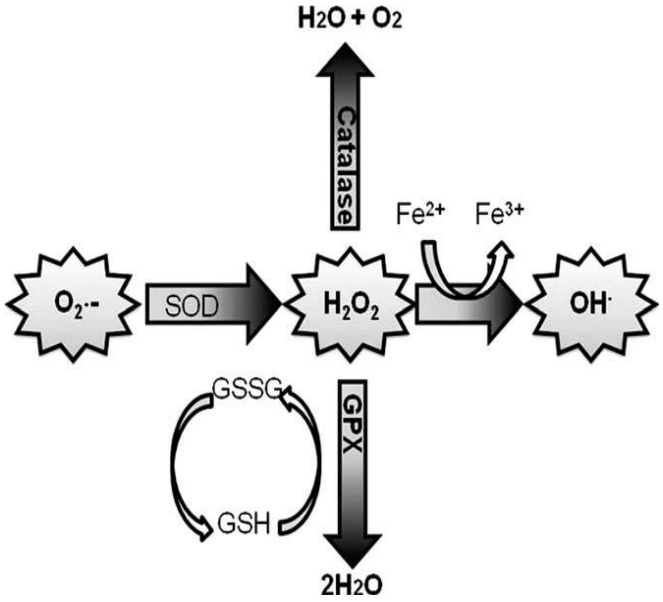
DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.5(3).657-65

Excess generation of these oxygen free radicals and oxidants generate a phenomenon called oxidative stress which cause oxidative damage to biomolecules resulting in lipid peroxidation, mutagenesis and carcinogenesis. Reactive oxygen species plays an effective role in the pathogenesis of different pathological diseases including cancer [3, 4]. Free radical induced lipid peroxidation causes a loss of cell homeostasis by modifying the structure and functions of cell membrane.

The most important characteristic of lipid peroxidation is to cause a considerable DNA-MDA adducts by interacting with cellular DNA [5, 6]. Reactive Oxygen species (ROS) are essential for multiple normal physiological processes like cell differentiation [7], apoptosis [8], cell immunity [9], and cellular defense against microorganisms [10] at low concentrations.

Antioxidants: To counteract ROS induced oxidative stress, aerobic organism rely on defenses, including enzymes (Superoxide dismutase, Catalase), as well as on small molecular weight endogenous antioxidants which include Reduced glutathione (GSH) and total Thiols (T-SH) [11, 12]. To this potential toxicity of free radicals the organism protects itself through different antioxidant defense systems [13]. The antioxidants neutralize the free radicals, stopping the chain of propagation and reducing their harmful effects on the body [14, 15].

In the case of a weakening of such an antioxidant defense or excess production of free radicals, a state of oxidative stress occurs [16]. Superoxide dismutase enzyme converts highly toxic superoxide molecules in to less toxic hydrogen peroxide molecule, Catalase enzyme converts hydrogen peroxide in to water and oxygen molecule. Other than enzymatic antioxidants some non-enzymatic antioxidants (Vitamin A, C and E) are also present to protect cells from oxidative damage.



- Balance of ROS and antioxidants. Oxidative stress is the imbalance between the production of ROS and antioxidants. The antioxidant properties of GPX, SOD, and Catalase control the production of oxygen species.

Abbreviations: GPX, Glutathione Peroxidase, GSH, Reduced glutathione; GSSG, glutathione disulfide; H2O2, hydrogen peroxide; O2_2, superoxide; _OH, hydroxyl radical; ROS, reactive oxygen species; SOD, Superoxide dismutase [17].

Oxidative stress in various types of Cancers:

1. **Oxidative stress in ovarian cancer:** In India, 15% of all gynecological cancers are ovarian malignancies [18]. It has the highest mortality rate amongst all gynecologic malignancies [19, 20]. Early diagnosis of ovarian malignancy is most important for better prognosis. A high manifestation of suspicion, better screening modalities and acknowledgment of high risk factors help to detect ovarian malignancy earlier [21]. Reactive oxidants (hydroxyl radicals, superoxide radicals, hydrogen peroxide, and singlet oxygen) generated during the mechanics of ovulatory follicular rupture, damage the DNA of ovarian surface epithelial cells that are located within limited diffusion radius [22].

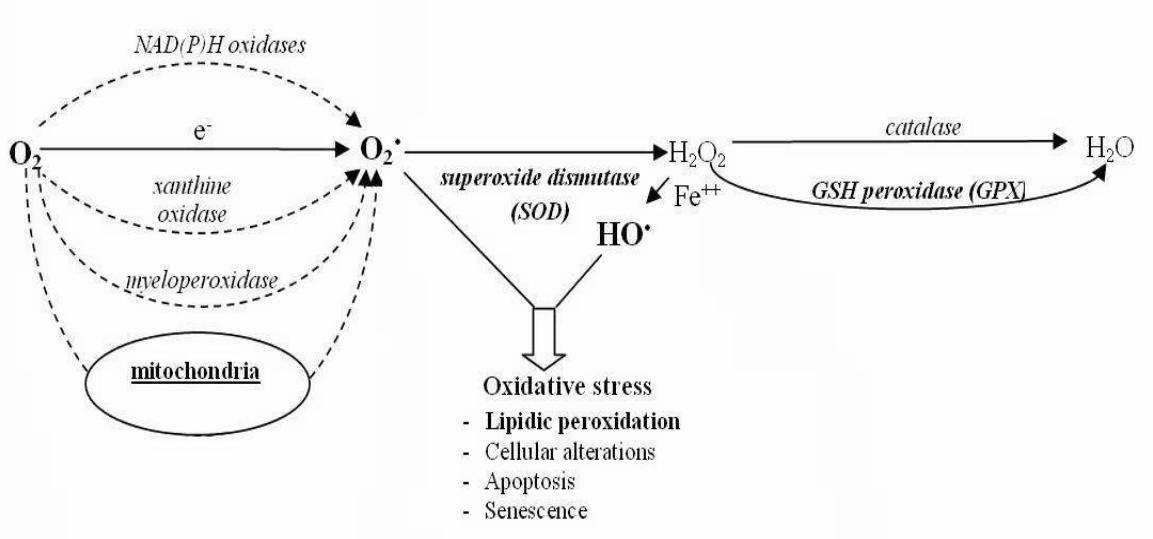
   Latest molecular studies have shown that ovarian cancer has acquired genetic alterations of oncogenes and tumor suppressor genes such as BRCA1, p53, nm23 and K-ras, which may be due to inflammation and oxidative stress [23]. Increased levels of plasma Lipid peroxidation and lower levels of SOD, CAT, vitamin C and E were observed in ovarian cancer patients when compared with normal subjects, the low levels of antioxidants and increased levels of lipid peroxidation is due to increased levels of oxidative stress in ovarian cancer patients [24].

   A study on ovarian cancer patients found that serum levels of MDA(malondialdehyde) were found to be increased and levels of vitamin E and SOD are found to be decreased in ovarian cancer patients, the levels of oxidative stress is high in ovarian cancer patients with stage iv than patients with stage ii ovarian cancer [25]. Considerably increased concentrations of plasma TBARS (Thiobarbutyric acid reacting species) and CD (conjugated dienes) and significantly lowered levels of SOD, CAT, vitamin C and vitamin E were observed in ovarian cancer patients as compared with normal subjects.

   The low levels of SOD, CAT, vitamin C and vitamin E in the plasma of ovarian cancer patients may be due to their increased utilization to scavenge lipid peroxides as well as their confiscation by tumor cells.

Increased levels of lipid peroxidation may be due to excessive oxidative stress caused by nonstop ovulation or epithelial inflammation [26].

2. **Oxidative stress in cervical cancer:** Cervical cancer is one of the most ordinary malignancies among women [27]. In India, cervical cancer ranks first among women cancers. The frequency of cervical cancer is very high among rural population and this could be due to changes in life style, personal hygiene and health care. Cervical cancer is generally associated with HPV infection [28]. Cancer of the cervix tends to arise during midlife in women, with half of the patients diagnosed between 25 to 65 years of age. It not often affects women under the age of 20 [29]. Cervical cancer is said to be mediated by Human Papilloma Virus (HPV) but recent data published also revealed role of oxidative stress in cervical cancer [30]. Levels of myeloperoxidase, Superoxide dismutase, Catalase, Reduced glutathione, Glutathione Peroxidase and Ascorbate were decreased in cervical cancer patients which further increased during radiotherapy [31].



O_2-• = superoxide radical, H_2O_2 = Hydrogen peroxide, •OH= hydroxyl radical

- Production of reactive oxygen species and the enzymatic defense mechanism against oxidative stress damage [32]. Increased values of lipid peroxide, nitric oxide and Copper were observed, whereas the activity of RBC-Superoxide dismutase, levels of Vitamin-C and Zinc were significantly decreased in cervical cancer patients as compared with controls group of healthy individuals of same age, also Cu/Zn ratio was found to be altered in cervical cancer patients. Oxidative stress is induced among cervical cancer patients, which increases the risk of cervical cancer [33]. Plasma MDA was found to be increased in cervical cancer patients when compared with controls. Glutathione peroxidase activity was increased while superoxide dismutase and Catalase activity was decreased in patients when compared with controls. Oxidative damage as demonstrated by the level of MDA is markedly increased in patients with changes of enzymatic antioxidants observed [34]. Manju *et al*. (2002) found Low levels of SOD and CAT in the circulation of cervical cancer patients may be due to their increased utilization to scavenge lipid peroxides as well as confiscation by tumor cells. Higher levels of TSA, AST, ALT and ALP, in the circulation of cervical cancer patients may be used in the diagnosis and treatment monitoring of patients with cervical carcinoma [35].

Erythrocytes from patients, despite of disease state, pre-malignant (low squamous intraepithelial lesion—LSIL and high squamous intraepithelial lesion—HSIL) or cancer, showed a significant 2–3 times increase in TBARS levels. Plasma vitamin C was lower in the carcinoma group. The reactivation index of δ-aminolevulinate dehydratase (δ-ALA-D) was higher in the patient group, when compared to control [36].

Plasma as well as erythrocyte MDA and plasma NO levels was higher in cervical cancer as compared to healthy controls, also antioxidant enzymes, Superoxide dismutase, Catalase and Glutathione peroxidase activities, were decreased whereas glutathione S-transferase activity was increased in cervical cancer patients [37].

3. **Oxidative stress in Oral cancer:** Oral cancer is a major form of cancer worldwide and is one of the most common malignancies in India accounting for 30-40 per cent of all cancers [38]. Subapriya *et al* (2002) have reported enhanced lipid peroxidation with decline in antioxidants in venous blood of patients with oral squamous cell carcinoma at different intraoral sites [39].

   Levels of plasma and erythrocytes lipid peroxidation TBARS are increased and levels of plasma and erythrocytes vitamin E, Reduced glutathione, Glutathione peroxidase, Super-oxide dismutase and Catalase are found to be decreased, TBARS levels increases and antioxidant levels goes on decrease with increase in the stage of the oral cancer [40]. Increased levels of lipid peroxidation with decrease in levels of antioxidants such as Superoxide dismutase, Catalase, reduced glutathione and Glutathione peroxidase was observed in the venous blood of oral squamous cell carcinoma patients as compared with the healthy controls, represents the increased levels of oxidative stress in oral cancer patients [41]. A study on oral cancer patients found that Lipid peroxidation products like lipid hydroperoxide (LHP) and malondialdehyde (MDA) and nitric oxide products like Nitrite (NO_2^-), Nitrate (NO_3^-) and Total nitrite (TNO_2^-) were significantly elevated, whereas enzymatic and non-enzymatic antioxidants were significantly lowered in oral cavity cancer patients when compared to normal healthy subjects [42].

4. **Oxidative stress in Breast cancer:** Breast cancer is one of the most frequent cancers in women of the developed and developing countries. Experimental investigations in addition to clinical and epidemiological studies associate the involvement of oxygen derived radicals such as singlet oxygen, superoxide anions ($O2•^-$), hydrogen peroxide (H2O2) and hydroxyl radical (OH•) in the etiology of cancer [43,44]. There is accumulating facts from animal and human systems implicating a role of oxidative stress and lipid peroxidation in the development of breast cancer [45]. Lipid peroxidation was found to be significantly increased in tumor tissue in breast cancer, the activity of antioxidants such as SOD and GPO were significantly elevated while the activity of Catalase was significantly decreased in cancer tissue compared with the nonmalignant breast tissue [46]. The serum levels of Uric acid and Bilirubin (markers of oxidative stress) are found to be increased in breast cancer patients at different stage of the cancer, when compared to the normal individuals [47].

   A study done by Gupta *et al* (2012) found that MDA and Nitric oxide levels were increased in breast cancer patients compared to the healthy subject group. Total cholesterol and triglycerides were elevated; and HDL-cholesterol level was found to be decreased in the cancer patients as compared to the healthy subjects, also the serum TAC (Total antioxidant capacity) levels and activity of SOD and GSH-Px were found to be decreased in the breast cancer patients as compared to the healthy controls [48]. The levels of Lipid peroxidation and nitrite were found to be increased in breast cancer patients when compared with normal individuals; their levels are increased significantly from stage iii to stage iv. The levels of vitamin E were found to decrease, levels of serum triglycerides are increased and HDL-cholesterol levels are decreased in breast cancer patients [49]. Breast cancer patients had an early increase of AGEs (advanced glycation end-products), marker of the carbonyl stress followed by further increase of AGEs and elevation of AOPP (advanced oxidation protein products), marker of oxidative stress in patients with progressive disease [50].

5. **Oxidative stress in Lung cancer patients:** Although lung cancer was a rare disease at the beginning of the 20th century, it has risen in parallel with an increase in cigarette smoking, becoming the most common type of cancer globally [51].

Murray and colleagues reported that lung cancer ranks as the tenth cause of death worldwide in 1997 and has led to 1 million human deaths per year. It is predicted that it will rise to the fifth cause of death by 2020 [52]. Recently, lung cancer prevalence has risen to 12.8% of all cancer cases and is responsible for 17.8% of all cancer deaths [53].

There is a significant increase of H_2O_2 and reduction in antioxidant capacity in the Exhaled breath condensate (EBC) of lung cancer patients shows the imbalance between levels of oxidants and antioxidants in lung cancer, which leads to increased oxidative stress. Oxidative stress is implicated in the development of lung cancer and may be an early marker of the disease [54]. In Adinocarcinoma, increased Glutathione content and NAPDH oxidase activity, and decreased Myeloperoxidase activity with decreased levels of 8-oxo-dG (a marker for DNA damage) are found, the level of oxidative stress and antioxidant defense seems to be different between adenocarcinoma and squamous cell carcinoma [55].

The study enclosed 152 lung cancer patients and 210 controls, indicated decreased Selenium (Se) concentrations and lowered activity of erythrocyte antioxidant enzymes (Glutathione peroxidase, Superoxide dismutase, Glutathione-*S*-transferase) in the blood of lung cancer patients, as well as significantly increased concentrations of vitamin E in erythrocytes and thiobarbituric acid reactive substances in the plasma of the study population. Low plasma Se concentrations enhance the estimated risk of lung cancer [56].

MDA level and DNA damage rate(8-OHdG) was higher in lung cancer patients than in the control group; in contrast, the coq10 enzyme level was significantly lower in lung cancer patients [57]. Serum MDA levels in Lung cancer and tuberculosis patients were much higher than in healthy controls. The SOD activity in serum from patients with lung cancer was markedly lower than tuberculosis and healthy groups, activities of SOD in lung cancer group significantly decreased as compared to the tuberculosis group [58].

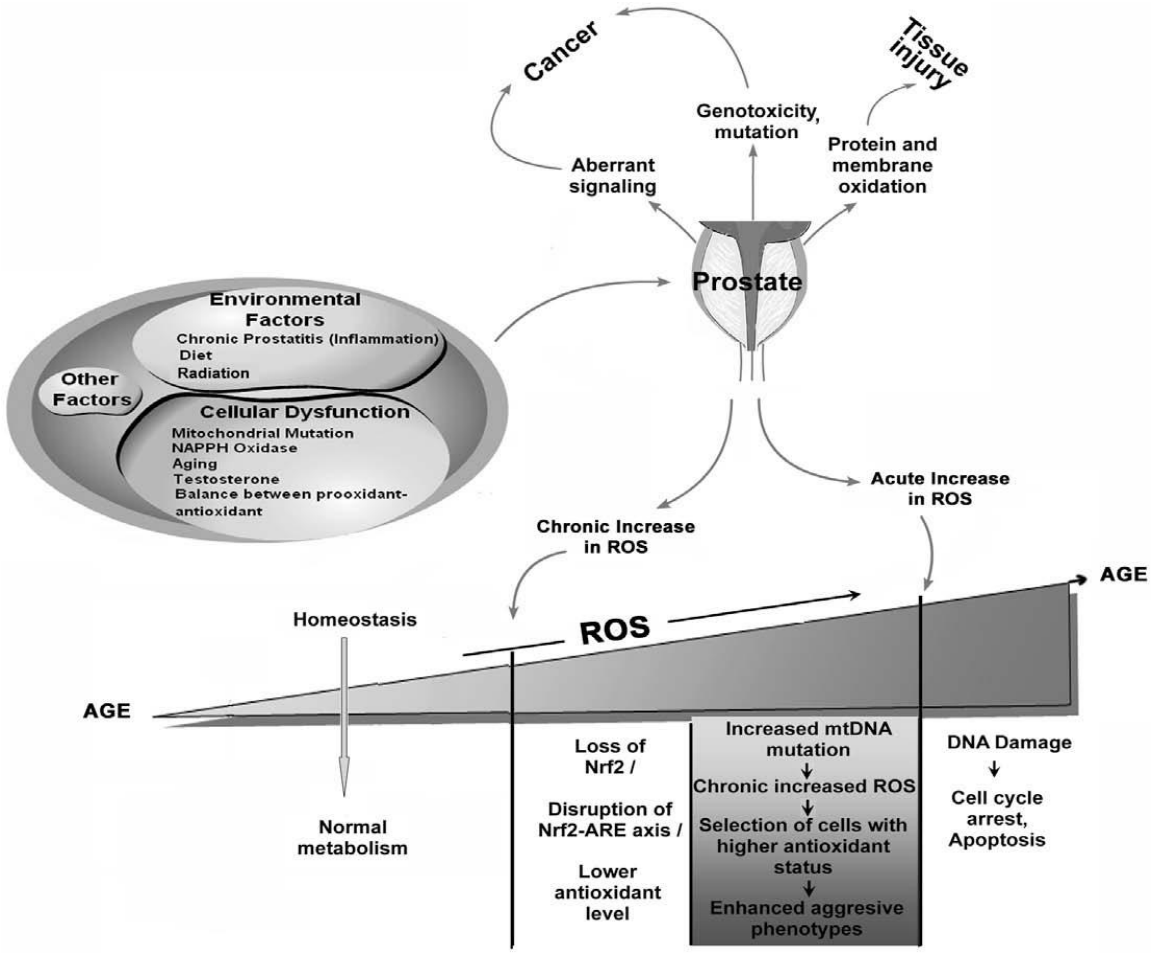
6. **Oxidative stress in Leukemia:** Chronic myeloid leukemia (CML) is characterized by neoplastic proliferation of hematopoietic cells. It is the first human malignancy where a specific marker, the Philadelphia (Ph) chromosome, was associated with CML [59]. At the gene level, breaks occur in the ABL and BCR genes on chromosome 9 and 22 respectively [60].

   In leukemia patients the plasma malonyldi-aldehyde and protein carbonyl levels were found to be elevated in both chronic phase (CML-CP) and accelerated phase (CML-AP) as compared to healthy volunteers, also the antioxidant status was found to be decreased in Chronic myeloid leukemia patients shows oxidative stress may be associated with the pathophysiology of Chronic myeloid leukemia [61]. The T-AOC (Total antioxidant capacity) and concentrations of Glutathione peroxidase, Superoxide dismutase, and MAO (Mono amine oxidase) were lower and the concentrations of AOPP (advanced oxidation protein products), MDA (Malodealdihyde) and 8-OHdG were also higher in acute myeloid leukemia patients then healthy individuals [62]. An imbalance in the antioxidant/prooxidant equilibrium in early stage leukemia patients with a significant higher SOS than that of the healthy control group have been observed [63].

7. **Oxidative stress in Prostate cancer:** Prostate cancer is the most frequently diagnosed noncutaneous malignancy in males, statistics from the American Cancer Society project 186,000 new cases and 28,000 deaths in US for the year 2008 [64]. Prostate cancer is a major age related malignancy with most incidences occurring between 54 and 75 years and rapid onset after 45 years [65, 66].

   Differences in prostate cancer incidence among various races, environment, diet, life style, genetic constitution and hormone of an individual/community are some of the contributing risk factors for occurrence of prostate cancer [67–69]. Studies highlighted the altered prooxidant–antioxidant status in prostatic tissue of man, rat and also in cell lines, where the imbalance between these antagonist

played a major role in the initiation of prostate carcinogenesis [70]. Recent studies suggested that Nrf2 and several of its target genes are significantly down regulated in human prostate cancer and as a result, cells were continually exposed to increased oxidative stress and may have resulted in their progression to metastatic disease [71].



- Mechanisms of ROS production, and cellular response to ROS in prostate cells: many factors both intrinsic to the cells and to external environment can lead to higher ROS production in the prostate. Increased ROS levels can lead to prostate dysfunction which in turn leads to more ROS production. An enzymatic or non-enzymatic antioxidant defense system counteracts and regulates ROS level to maintain physiological homeostasis. Lowering ROS level below the homeostatic point may interrupt proliferation and host defense system, while accumulative ROS in prostate can alter normal functioning of the prostate leading to low antioxidant level [by disrupting Nrf2-antioxidant response element axis (ARE)], increase mtDNA mutation and aggressive phenotypes, and caused DNA damage [72].

Recent research has also thrown light on GSH peroxidase enzyme which catalyzes the neutralization of peroxide via glutathione redox system. Circulating levels of GSH peroxidase in the plasma as well as in the prostate tissue are markedly decreased in prostate cancer biopsy specimens from patients [73, 74].

8. **Oxidative stress in Gastric cancer, Colon cancer and some other cancers:** The blood serum of 94 untreated cancer patients with various localization of the tumors (gastric cancer, colon cancer, breast and ovarian cancers, hemoblastoses); it has been found that all examined patients had increased levels of SOD and MDA in normal values of catalase activity. The use of Selenium in postoperative patients with tumors of the liver increased selenium levels by 10–12%.

This was accompanied by a decrease in the content of SOD and NOx, and earlier recovery of detoxification and synthetic liver function. These findings point to intensification of oxidative stress and metabolic disorders in the malignant process, which is the basis for prescription of metabolic correction therapy [75].

SUMMARY: Oxidative stress is the condition of imbalance between the generation of free radicals and antioxidant defense system present in the cells to minimize the toxicity caused by free radicals in the cell. It has been shown above in the review that there is a condition of oxidative stress generated in patients of Oral cancer, Breast cancer, Cervical cancer, Lung cancer, ovarian cancer, Leukemia, Prostate cancer, Gastric cancer and Colon cancer. Oxidative stress a marker of tissue damage is found to be increase with the progression of the cancer which can be measure by the levels of Lipid peroxidation and various antioxidants in serum of cancer patients.

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How to cite this article:
Sharma S Shrivastav A and Shrivastav BR: Clinical evidences of Oxidative stress as a Biomarker in various types of Cancers:: A Review. *Int J Pharm Sci Res* 2014; 5(3): 657-65.doi: 10.13040/IJPSR.0975-8232.5(3).657-65