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# IMPACT OF OXIDATIVE STRESS IN THE PATHOGENESIS OF CERVICAL CANCER: THERAPEUTIC APPROCHES

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## ABSTRACT

Cervical cancer (CC) is acknowledged as the most ubiquitous carcinoma among females along with the utmost prevalence in developing nations. The major cause of CC is HPV exposure, especially HPV16 and 18. Inflammation is linked to the carcinogenesis of CC in addition to HPV infection. Although the precise cause of CC is yet unknown, using oral contraceptives, being immunosuppressed, and smoking may enhance the risk of the disease. Oxidative stress (OS), in addition to HPV, is linked to cervical cancer. Across several clinical and preclinical research, the dysfunctional redox system and the impact of oxidative stress throughout the aetiology of CC have been examined. Redox homeostasis must therefore be maintained, which calls for both enzymatic and nonenzymatic redox regulators. In this study, we explored the therapeutic strategies used to preserve redox balance, lower cervical cancer mortality, and illustrate the contribution of oxidative stress in the aetiology of the disease.

**KEYWORDS:** HPV, Cervical cancer, ROS, RNS, Inflammation.

## INTRODUCTION

The furthermost common malignancy in almost altogether low-resource nations, cervical cancer (CC) is a severe threat to females' health and a major global health issue. Nearly 569,847 new instances of CC were detected worldwide, and CC caused 311,365 fatalities (1). CC is the second most common cause of death for females in India, according to the National Institute of Cancer Prevention & Research (NICPR). According to GLOBOCAN 2018, approximately 96,922 women in India receive a new diagnosis of CC each year, and 60,078 of them pass away. Based on current incidence rates, it is predicted that by 2025, there would be 225,000 new cases annually in India (2-3). High-risk human papillomavirus (hr-HPV) infection, particularly HPV 16 & 18, is universally acknowledged to be the cause of CC (4-5). Although HPV vaccination has contributed to a reduction in the incidence and prevalence of CC, developing countries struggle to implement nationwide vaccination programmes due to the associated high costs (6). Diversifying CC prevention strategies is crucial. According to estimates, HPV DNA is present in 85% of pre and 90% of malignant squamous lesions in the uterine cervix (7). With over 90% of the time, particularly in younger women and adolescents, the immune system is able to eradicate HPV virus following 2 years of infection (8). There are still a limited number of HPV infections, a few of which progress to malignancy. Cervical intraepithelial neoplasia (CIN), a non-invasive precursor lesion that is distinguished with variable degrees of cellular atypia (dysplasia), seems to be the primary cause of CC (9). Three different kinds of CIN have been identified: CIN1, which exhibits mild dysplasia; CIN2, which exhibits moderate dysplasia; CIN3, or carcinoma in situ, which exhibits severe dysplasia and might progress to invasive squamous cell carcinoma (SCC) 9. In addition, cervical adenocarcinoma has been associated to alterations in the cervix's glandular epithelium of the brought on via HPV and other cofactors (10).

Additionally, HPV infection is not enough to cause CC; rather, the condition is caused by a complicated aetiology (11), within oxidative stress (OS) probably being a major factor in the development of CC (12-13). Oxidative stress has been identified as a risk factor for chronic inflammation, atherosclerosis, diabetes,

ischemia-reperfusion injury, and different cancers (14-15). Known risk factors for CC include smoking,(16) tar exposure, (17) HPV infection, (18) coinfection with other viruses such herpes simplex virus-2 (HSV-2), (17) STDs, and lifestyle. Other co-factors that affect the development of CC include early sexual initiation, low socioeconomic position, having several sexual partners, multi-parity, immunosuppression, and the use of oral contraceptives (19).

be created when NO and O2− interact (22). The structure and functionality of proteins, carbohydrates, lipids, and nucleic acids in cells are adversely affected by an excess or overproduction of ROS, which can be brought on by endogenous (23) and or external sources like as illness, smoking, and metabolic activities (24). Disruption to these macromolecules has an impact on a number of cellular functions, including angiogenesis, cell proliferation, migration, apoptosis,

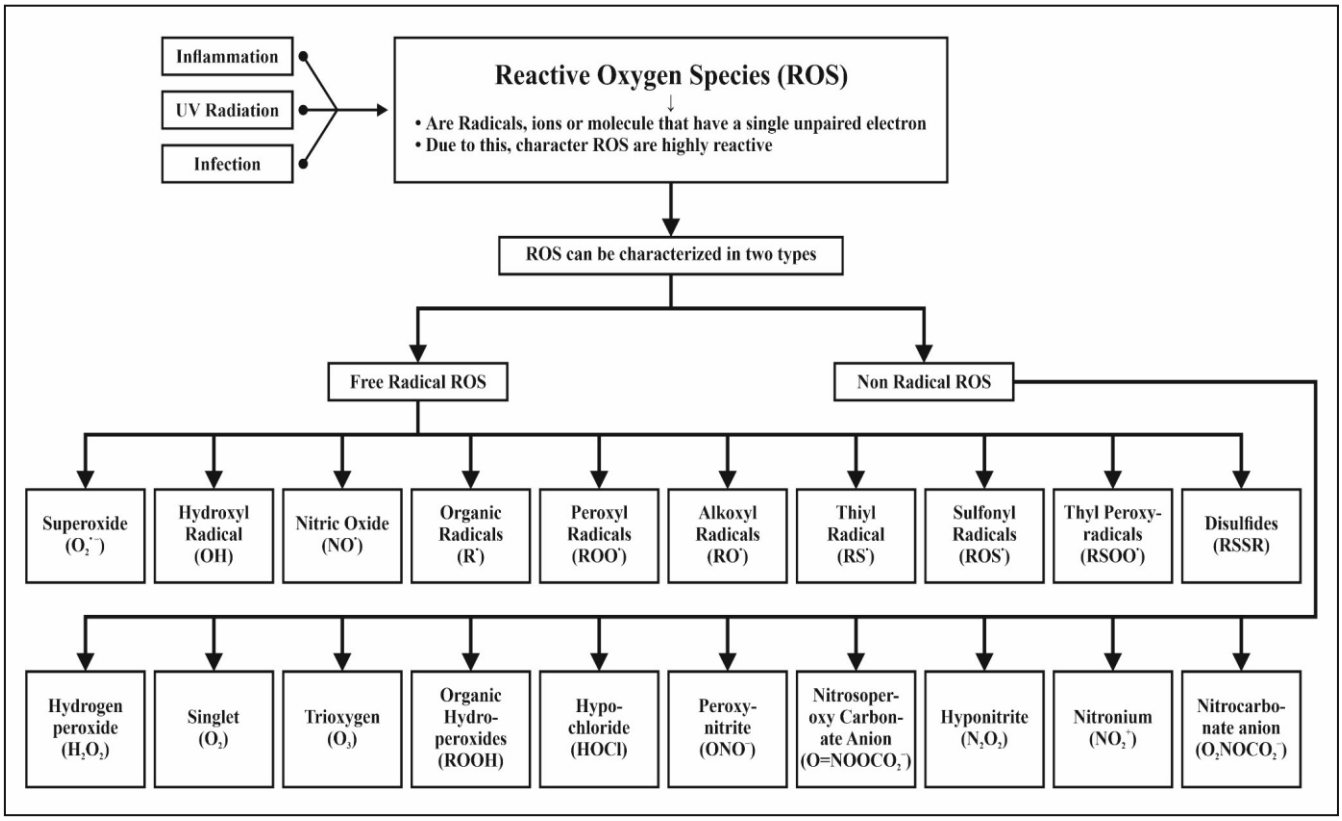


***Fig. 1: Showing Generation and Categorization of free Radical***

"A discrepancy in the production and elimination of superoxide anion" is the essence of oxidative stress. On the contrary perspective, oxidative stress is brought on by "A mismatch in the prooxidant-antioxidant system." A decrease in antioxidant levels culminates in more free radicals, which damage DNA, induce numerous dysfunctions, and ultimately in disease (20). ROS (Reactive oxygen species) such as O2 (superoxide anion), H2O2 (hydrogen peroxide), and OH (hydroxyl radical), which are all shown in fig. 1, (21) are produced in excess as a result of the partial reduction of ambient oxygen. Nitric oxide (NO), a free radical produced by L-arginine and a potent vasodilator, is overproduced inside the body and is made easier through raised NO concentrations. Additionally, peroxynitrite (ONOO−), a compassionate of reactive nitrogen species (RNS), can

and resistance to treatment, and contributes to the aetiology of cancer (25).

**Source of ROS production**

**Endogenous**

Numerous intracellular structures, including the mitochondria, endoplasmic reticulum (ER), peroxisomes, nuclei, cytoplasm, plasma membranes, and even extracellular regions, create ROS. In the majority of human cells, the electron transport chain (ETC) is where ROS are primarily produced (26). The generation of ROS is catalysed by several enzymes, some of which are listed in fig. 2, including NADPH oxidase (NOX), isoform of NADPH oxidase, lipoxygenases (LOXs), xanthine oxidase (XO), myeloperoxidase (MPO), glucose oxidase (GO), and cyclooxygenases (COXs) (27).

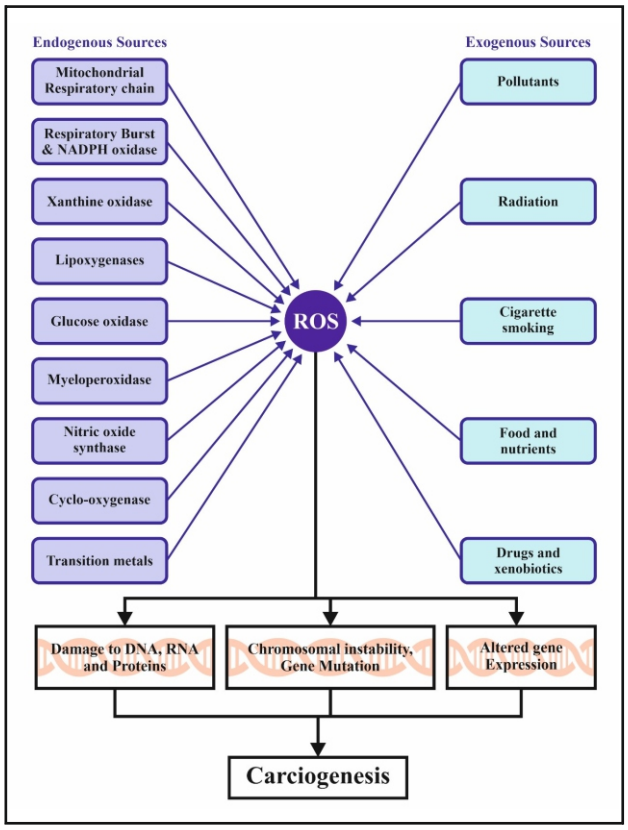


***Fig. 2: Sources for Production of Reactive Oxygen Species (ROS)***

### Exogenous

Numerous extrinsic factors of ROS contribute to oxidative stress and can either directly or indirectly affect gastrointestinal reflexes (GIT) (28). Oxidative stress can be brought on by xenobiotics, tobacco smoke, air pollution, water pollution, foods and pharmaceuticals, ionising and nonionizing radiation. Examples of exogenous sources of ROS are heavy metal exposures including arsenic, lead, chromium, cadmium, and mercury, organic solvent exposures, chemical agents like quinones, and pesticide exposures showed in fig. 2 (29). Various clinical and preliminary studies have investigated the pathogenic effects of oxidative stress and the dysregulated antioxidant system in CC. In this review, we attempted to provide a summary of the role of OS in the development of CC and chemotherapy and radiotherapy resistance. By comprehending this, new methods to lessen therapy resistance and enhance CC diagnostic and therapeutic procedures can be developed.

## OXIDATIVE STRESS AND CERVICAL CANCER PATHOGENESIS

The most prevalent indicator of oxidative stress (OS) is the oxidant-antioxidant adduct malondialdehyde (MDA), which is present in cancer patients. ROS, which are created as a result of various processes that produce too much MDA and disturb normal cell activity, cause lipid peroxidation, which induces cancer (30). Excessive ROS levels result in damage to DNA, lipids, and proteins, inactivation of tumour suppressor genes, and enhanced proto-oncogene expression summarized in fig. 2 (31). Research on the impact of genetic/epigenetic variables on CC risk is scarce 17, despite the fact that the impact of external factors on CC is well recognised. It has been demonstrated that the generation of ROS promotes viral spread (32). When HPV16 and 18's viral genomes are integrated into the host genome, viral oncogenes including E6 and E7 are overexpressed. The tumour suppressor proteins p53 and pRb, respectively, are suppressed by this E6 and E7, which results in CC transformation (33-34). A key factor in HPV carcinogenesis is HPV integration, which can be improved by inflammation and oxidative stress (35). Leukocytes are stimulated by HPV infection and produce a range of cytokines and chemokines into the bloodstream, which sets off inflammatory reactions (36). As a result, the HPV-induced inflammatory state can increase the production of ROS in macrophages and polymorphonuclear neutrophils (37). Both DNA double-strand breaks (DSBs) and DNA damage are induced by ROS, and both are necessary for the amalgamation of viral DNA into host genomes leads the induction of carcinogenesis (35). According to Chen et al, the glutathione synthesis inhibitor buthioninesulfoximine (BSO) persistently induces oxidative stress in human cervical keratinocytes that damages DNA and speeds up HPV integration (38). Williams et al. discovered that E6*, a shorter version of E6, enhances the quantity of ROS which increases DNA damage in cells taken from human cervical carcinomas (39). Wang et al. discovered that E6 targets p53 in cervical cancer cells to reduce the expression of the tumour suppressor microRNA miR34a (40). Thiobarbituric acid reactive substances (TBARS) and Conjugated dienes, both consequences of lipid peroxidation, were found to be present at higher plasma levels, according to Manju et al (41). When compared to controls, researchers observed that women with CC had lower levels GSH, GST, GPx, SOD, and non-enzymic antioxidants such ascorbic acid (vitamin C) and alpha tocopherol (vitamin E). When compared to healthy controls, serum levels of vitamin C, zinc (Zn), and the lipid peroxidation marker MDA were all significantly lower in CC patients than in controls, according to research by Naidu et al (42). According to Palan et al., plasma concentrations of natural antioxidant including alpha and beta carotene, Vit E were significantly lower in females with

dysplasia or cancer, proven histopathologically than in controls (43). Decreased intensities of enzymatic and non-enzymatic regulators of redox state may be caused by oxidative damage to enzymes, a lack of essential trace elements, nutritional inadequacies, and increased antioxidant use to inhibit ROS production (44). The study also revealed reduced levels of glutathione, Ascorbic acid and vitamin E, as well as antioxidant enzymes. They proposed that the development of cervical cancer is associated with oxidative stress and inadequate antioxidant concentrations (45).

neutralize the radical forms of other antioxidants like glutathione and vitamin E. Vitamin C can be freely generated from Asc using the enzyme NADH or NADPH dependent reductases. A number of antioxidants have the ability to directly interact with ROS and/or free radical intermediates (FRI) generated by ROS, stopping the chain reaction and reducing ROS-induced damage (46).

Naturally occurring substances with chemo-preventive and chemotherapeutic capabilities, as well as antioxidant characteristics have recently received much

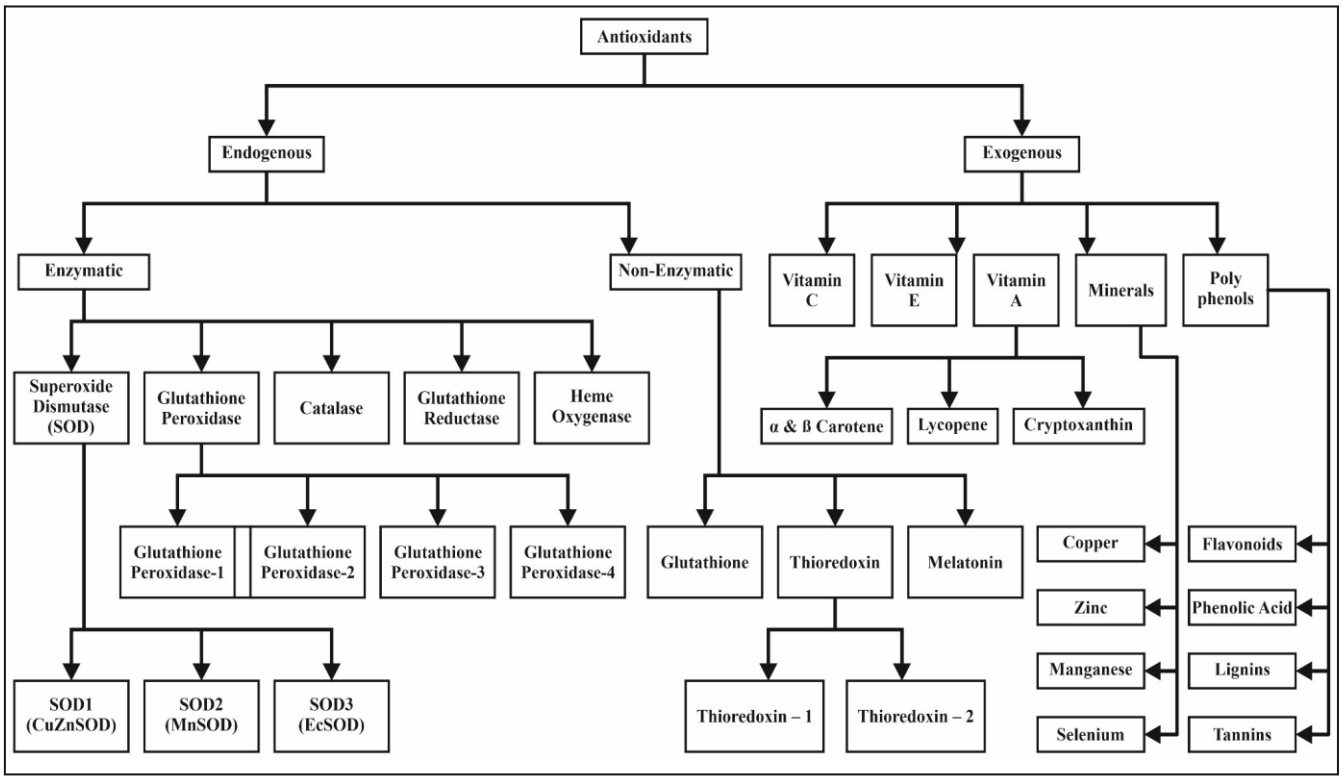


***Fig. 3: Source of Antioxidants for Neutralizing Free Radicals.***

## THERAPEUTIC APPROACHES

Antioxidants are compounds that could really remove the unbalanced state of free radicals by either giving or taking electrons from the radicals. Antioxidant compounds can either directly interact or neutralize highly reactive free radicals, or they can change into new free radicals that are less reactive, have a longer half-life, and pose a lower risk than the original radicals they have neutralized. These free radicals may be neutralized by more antioxidants or by different methods, which would end their radical state. For instance, many antioxidants have aromatic ring structures and have the ability to delocalize their unpaired electron. Both vitamin C and vitamin E react with or neutralize free radicals. Ascorbic acid, a precursor of vitamin C, can also rejuvenate and

interest summarized in fig. 3 (47). Furthermore, studies have indicated that natural chemical found in plant extracts including phenolic compounds can make tumor cells more sensitive to radiotherapy and chemotherapy (48). These findings suggest that natural antioxidants may have the ability to slow the onset and progression of precursor lesions. Molecules with these characteristics could be utilized as a supplementary for cancer (49). Folate, a water-soluble B vitamin is necessary for nucleotide synthesis and hypomethylation of DNA (50). Vitamin B6 is intended to help regulate the immune system, which has been associated to an enhanced risk of cancer51. Vitamin K has anticancer properties and promotes apoptosis in cancer cells (52-53). Niacin has also been shown to protect against cancer recurrence in recent studies (54-55).

## CONCLUSION

Cervical cancer is the extreme fatal malignancy among females. Substantial investigation, better clinical consequences have yet to be attained. This unsatisfactory outcomes can be attributed to a lack of knowledge concerning cancer biology. As a consequence, it is necessary to understand what molecular pathways are involved in tumorigenesis. This review summarizes the role of OS in the cervical cancer pathogenesis and their therapeutic approach. Oxidative stress caused by ROS can cause DNA and protein damage, which leads to genomic instability and promotes the growth of tumours. Furthermore, it has been demonstrated that oxidative damage to molecules and reduced antioxidant levels are present in CC patients. Based on the findings of numerous authors, redox regulating approaches may be regarded as a unique therapeutic approach for the treatment and/or prevention of cervical cancer. In fact, numerous clinical and preclinical studies have shown that addressing the redox status of cervical cancer with antioxidants can lower the formation of free radicals like ROS and RNS.

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