

How to Cite:

Aljurany, A. N. H., & Samarrai, O. R. A. (2022). Evaluation of chemokine CXCL12 level with oxidative stress in breast cancer. *International Journal of Health Sciences*, 6(S3), 6382–6392. <https://doi.org/10.53730/ijhs.v6nS3.7414>

Evaluation of chemokine CXCL12 level with oxidative stress in breast cancer

Ali Nassrullah Hussein Aljurany

Department of Chemistry, College of Education, University of Samarra, Samarra - Iraq

Corresponding author email: alialjuranyali@gmail.com

Othman Rashid Al Samarrai

Department of Chemistry, College of Education, University of Samarra, Samarra - Iraq

Abstract--Cancer is a major public health problem worldwide, and cancer is a term given to a group of diseases characterized by abnormal growth and proliferation of cells as a result of uncontrolled cell divisions or tumor suppressor genes. The current study was included an evaluation of chemokine CXCL12 level with oxidative stress in women with breast cancer. The study included the collection of 90 blood samples for women, and the samples were distributed into 50 samples for women with breast cancer, their ages ranged from 40-70 years, the samples were collected from the Breast Cancer Center in Baquba General Hospital, and 40 blood samples for healthy women as a control group, and their same ages, during the period from the beginning of October 2021 until the end of December 2021. The results showed that there was a significant increase in the level of chemokine CXCL12 in women with breast cancer compared to the healthy women. Also, showed a significant increase in the level of malondialdehyde and nitric oxide, with a significant decrease in the level of Glutathione in the women with breast cancer woman compared to the healthy women.

Keywords--breast cancer, chemokine CXCL12, malondialdehyde, nitric oxide, glutathione.

Introduction

The breast is one of the organs of the female reproductive system and it consists of skin, subcutaneous tissue, blood, lymph vessels, and nerves (1). The breast is divided into 15 to 20 lobules and is placed at the top of the chest muscles that cover the ribs. The lobules contain many small globules, The lobules, in turn,

contain groups of tiny glands that can make milk, which runs from the lobules to the nipple via thin tubes known as ducts. Fat fills in the gaps between the lobules and ducts (2). Lymph vessels, which carry a clear fluid called lymph, are also found in the breast. These channels lead to lymph nodes, which are small, round organs found near the breast in the lower arm, above the collarbone, in the chest behind the sternum, and in a variety of other places, Bacteria, cancer cells, and other potentially hazardous substances in the lymphatic system are trapped in lymph nodes (2,3).

Breast cancer is one of the life-threatening diseases that may affect a woman's sense of self-respect, self-love, and sense of femininity (4), The most prevalent non-cutaneous malignant tumor is breast cancer (5). It is a type of cancerous tumor that occurs in the breast tissue and appears in the tubes. Which carries milk to the nipple (6), and occurs in women and men, but the infection rate in women is very large compared to males, as every 200 injuries in women correspond to one infection in men (7). Cytokines are peptides or glycoproteins with a low molecular weight between 20-25 kDa and are cellular media used in signal transduction and intercellular communication (8). These mediators are produced by immune cells and different types of cells and play an important role in innate and acquired immunity (9). Cytokines were first discovered in 1957 by the identification of interferon- α , which was identified as a protein that interferes with the immune response in viral infections (10).

The importance of Cytokines in the types of natural and acquired immunity, as it intervenes in many infectious and inflammatory diseases, injuries, infectious diseases and sepsis (blood poisoning), but its mission is not limited to the immune system only, as its role in communication between cells during genetic evolution is also great (11), and it helps to differentiation, proliferation and migration of immune cells and stimulating them to produce other compounds depending on the type of stimulus. Chemokines, which belong to the cytokine superfamily, are small molecular polypeptides produced by immune cells and have a molecular weight of 8-10 KD. Chemokines are divided into four subfamilies based on the amount and placement of N-terminal cysteine molecules: C, CC, CXC, and CX3C (12). Chemokine CXCL12 is a homologous CXC chemokine containing seven different forms consisting of 67 amino acids, molecular weight 1.061 g/mol, Stromal cells, fibroblasts, and epithelial cells all release it into a variety of tissues, and it regulates hematopoietic cell trafficking and secondary lymphoid tissue engineering (13).

Oxidative stress is generally defined as an imbalance between oxidants (free radicals and their products from metabolic processes) and antioxidants, as cells contain more oxidants than antioxidants, and oxidative stress occurs when the level of oxidative compounds exceeds the ability of antioxidants to remove them as. The production of oxidizing substances is greater than the ability of the cellular system to remove the effects of these radicals, whether their sources are internal or external, as the antioxidants are unable to neutralize these oxidizing factors, and the imbalance leads to an increase in the components of the internal reactions in the body, which leads to the destruction of cells, Increased generation of peroxides and free radicals can have hazardous effects. A state of oxidative stress can occur when antioxidants present in the body are reduced (14,15).

Materials and Methods

Samples and Blood Collection

Blood samples included 90 patients with breast cancer and healthy women, whose ages ranged between 70-40 years, the samples were collected from the Cancer Tumor Center at Baquba General Hospital in Diyala Governorate, for the period from 10/31/2021 to 11/21/21. 30. Then the samples were distributed according to the study design into two groups, the first group included 40 healthy women (control group), while the second group included 50 patients with breast cancer. Samples for the current study were collected by withdrawing 5 ml of venous blood from both patients and healthy women, where 5 ml of blood was taken and placed in test tubes and left for 10 minutes to coagulate, then the serum was separated from it using a centrifuge at 3000 rpm for 10 minutes, and then the separated serum was kept under freezing until used in serological tests.

Biochemical parameters analyses

The CXCL12 was determined by Enzyme Linked Immune-Sorbent Assay (ELISA) method, the ELISA kit providing by (MyBioSource, China), bearing the catalog No. MBS9135919, Malondialdehyde (MDA) was determined by ELISA method, the ELISA kit providing by (MyBioSource, China), bearing the catalog No. MBS263626, Nitric Oxide (NO) was determined by ELISA method, the ELISA kit providing by (MyBioSource, China), bearing the catalog No. MBS732723, and Glutathione (GSH) was determined by ELISA method, the ELISA kit providing by (MyBioSource, China), bearing the catalog No. MBS161025

Statistical analysis

The results of the current study data were statistically analyzed using the statistical program (SPSS) version (23) through the mean and standard deviation (SD), and using the T-test to determine the difference between the two groups at the level of probability ≤ 0.05 .

Results and Discussion

Table 1 shows that the mean \pm SD of chemokine CXCL-12 level was (906.04 ± 283.73) pg/ml in women with breast cancer, while it was (144.48 ± 73.32) pg/ml in the control group. The findings revealed a considerable increase in the concentration of the chemokine CXCL-12 in breast cancer patients compared to healthy women (Figure 1).

Table 1
Levels of biochemical parameters in Breast cancer patients and healthy women

Parameters	Control Mean \pm SD	Patients Mean \pm SD
CXCL-12 (pg/ml)	144.48 \pm 73.32	906.04 \pm 283.73*
MDA (nmol/ml)	0.72 \pm 0.08	1.85 \pm 1.00*
NO (μ mol /L)	12.13 \pm 2.95	21.02 \pm 5.62*

GSH ($\mu\text{ng/ml}$)	8.06 ± 3.93	$5.69 \pm 3.01^*$
---------------------------	-----------------	-------------------

* This sign means different significant at $P \leq 0.05$.

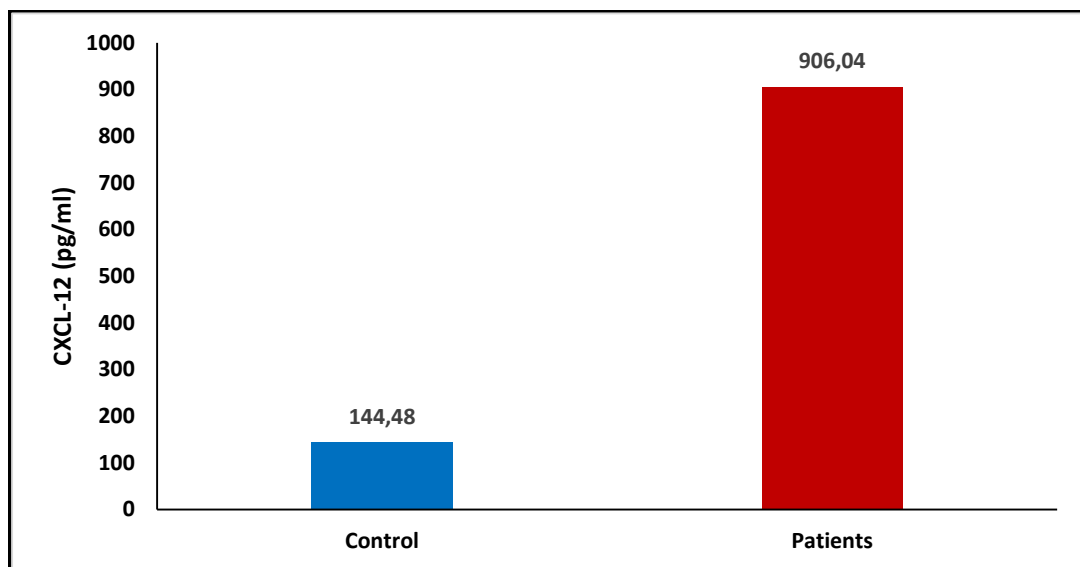


Figure 1. The CXCL-12 chemokine concentration in the blood serum of the two groups of patients and control

The current study's findings were consistent with Emilia et al findings (16) and Marina et al (17) and Dinesh K et al (18), who confirmed in their study the high level of chemokines for patients with breast cancer, especially the CXCL-12 chemokine that regulates breast tumor growth and promotes carcinogenesis by increasing vascular permeability and dilating infiltrating neoplastic vasculature. Breast cancer is a major public health issue, accounting for 3% of all deaths among women, according to the World Health Organization (19,20). Chemokines and their receptors have been shown to play essential roles in the development of cancer, including cell cancer proliferation, migration, and tumor immune cells, in several studies (21,22). As well as an according to a growing body of data, the chemokine CXCL-12 and its cognate receptor CXCR4 play a vital part in this process (23, 24).

It activates CXCR4 chemoreceptors, which help to improve clinical outcomes in a variety of solid cancers, including breast cancer (25,26). CXCL-12 secretion *In vivo* invasion and macrophage recruitment to the main tumor could be aided by breast cancer cells. CXCR4 signaling is required for enhanced invasion, which is most likely achieved by activating CXCR4 on tumor macrophages, resulting in greater paracrine contacts with tumor cells in the tumor microenvironment. CXCL-12 overexpression also leads to altered tumor architecture by increasing microvessel density, which can be mediated by tumor-associated macrophages (27). Table 1 showed the mean \pm SD of the MDA concentration, it was (1.58 ± 1.00) nmol/ml for patients with breast cancer, while it was (0.72 ± 0.08) nmol / ml for the control group. When compared to healthy women, the concentration of MDA in breast cancer patients was shown to be significantly higher, as in figure 2.

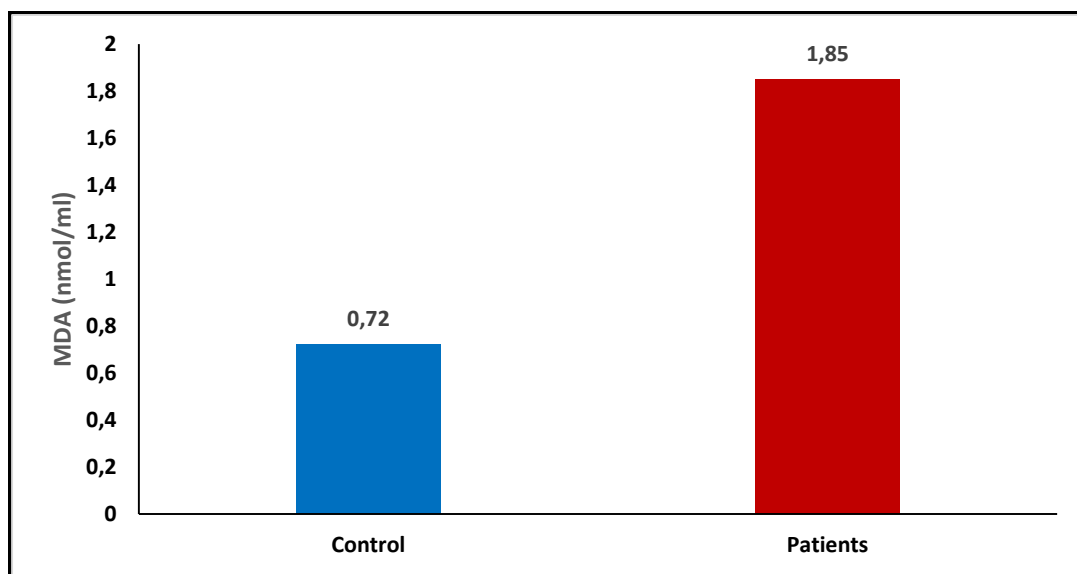


Figure 2. The MDA concentration in the blood serum of the two groups of patients and control

The current study's findings are consistent with those of Lilo et al. (28) and Khalaf et al. (29) and Nsaif, et al. (30). As MDA is the main product of lipid oxidation and is a toxic molecule that must be taken into consideration as not only a sign of lipid peroxidation, but it can interact with proteins and DNA leading to oxidative stress (31, 32). The concentration of MDA is a good indicator of the occurrence of lipid peroxidation and a vital evidence of some diseases, including some cancers and atherosclerosis (33), although its concentration increases when oxidative stress or some diseases occur, so it is more important to monitor the super-oxidation of fats and oxidative damage of ROS (34). MDA is one of the types of oxidative stress that is a major cause of the initiation and development of breast cancer and is often associated with a high risk of cancer, as the level of MDA is elevated in patients with breast cancer. This is usually associated with vital antioxidants that promote metabolism (35, 36).

Also, oxidative stress occurs in biological systems as a result of a mismatch between production and removal of reactions of free radicals, so the production of free radicals in large quantities, which is responsible for the events of many biochemical changes within cells, and also there are many factors that lead to the occurrence of oxidative stress, the most important of which are trauma, diseases carcinogenicity, heat, ionizing radiation, toxins and violent exercise (37,38) .The concentration of nitric oxide was measured in breast cancer patients and compared to healthy women without breast cancer as a control group, as shown in Table (1). Table 1 showed the mean \pm SD of the nitric oxide concentration, it was (21.02 ± 5.62) $\mu\text{mol/L}$ in patients with breast cancer, while it was (12.13 ± 2.95) $\mu\text{mol/L}$ in the control group. Additionally, the findings revealed a considerable increase in the concentration of nitric oxide in women with breast cancer compared with the healthy women, as in figure 3.

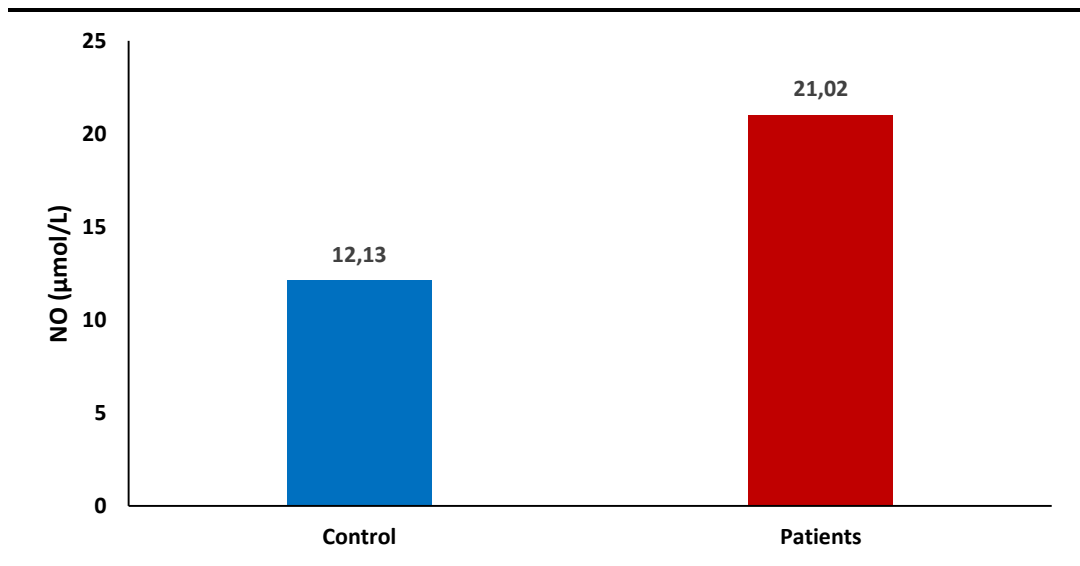


Figure 3. The nitric oxide concentration in the blood serum of the two groups of patients and control

The findings of the current study differed from those of Ashtee et al. (39), which showed in their study a decrease in the level of nitric oxide in the blood serum of women with breast cancer compared with the healthy group. Nitric oxide plays a dichotomous role in the development of cancer, depending on its concentration and location. It is a very fascinating chemical in the tumor microenvironment because of its primary and anti-tumor effects. Nitrogen oxide promotes carcinogenesis in low concentrations, but at greater concentrations, it becomes toxic to cancer cells and induces apoptosis through the creation of peroxynitrite (40). Nitric oxide (NO) is expressed in all different malignant carcinomas, tumor cell-derived NO promotes cancer progression, whereas NO produced by host stromal cells has a distinct effect, inhibiting the growth of nitrogen oxide-sensitive malignancies while enhancing the growth of NO-resistant tumors. (41). The significance of NO and NOS in cancer growth and development is gaining popularity, with research being conducted in a variety of cancer forms, including brain cancer. (41,42), pancreatic (43), and breast cancer, confirm its critical role in these different cancers (44,45). Patients with breast cancer had their concentrations measured, while healthy women without breast cancer served as a control group, as shown in Table (1). Table (1) showed the mean \pm SD of glutathione concentration, it was (5.69 ± 3.01) $\mu\text{ng/ml}$ for patients with breast cancer, while it was (8.06 ± 3.93) $\mu\text{ng/ml}$ for the control group. Figure 4 shows that the concentration of glutathione in women with breast cancer was much lower than in healthy women.

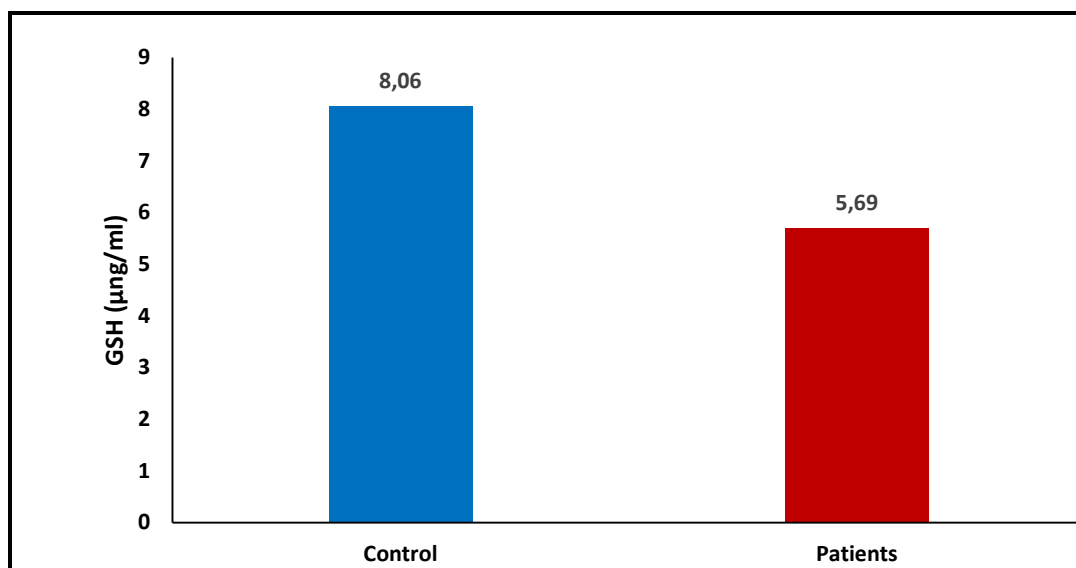


Figure 4. The glutathione concentration in the blood serum of the two groups of patients and control

The current study's findings were consistent with those of Enrico et al (46) and Chih-Ching et al. (47) and Luke et al. (48) as glutathione is one of the reducing agents because it contains a thiol group, which has the ability to endow a hydrogen atom (49). It is also an antioxidant, as it prevents and delays cell damage, and detoxifies chemicals within the liver (50), as well as an essential component of the defense system in plants and humans exposed to various environmental stresses. The protective mechanism includes sequestration of minerals and scavenging of reactive oxygen species by glutathione in plants which facing environmental pressures (51). Due to its effective participation in the prevention of oxidation, its level will decrease as a result of its consumption in cases of oxidative stress, as well as it will decrease in the animal's plasma and tissues with age, and the reason for this is that the process of protein synthesis is slow and less efficient with an inverse relationship between the concentration of glutathione In tissues and under oxidative stress (52). Antioxidant defense is another crucial purpose for glutathione, (Gene expression, DNA and protein synthesis, cell proliferation and signaling, cytokine generation, and immunological response) (53). Also, it works to reconstitute some antioxidants, including vitamin C, due to its importance as anti-oxidant. GSH preservation of cells from diseases that affect the organism, and it was found that glutathione protects the liver against the effects of radiation and chemotherapy (54). Glutathione deficiency causes oxidative stress, which leads to aging and causes a variety of disorders including seizures, Alzheimer's disease, Parkinson's disease, liver disease, cystic fibrosis, sickle cell anemia, HIV, AIDS, cancer, heart attack, stroke, and diabetes (55). Based on significant correlations between the reduced-to-oxidized glutathione (GSH/GSSH) ratio and redox homeostasis in cancer patients, the glutathione system may be the body's first line of defense against oxidative stress and for maintaining redox homeostasis (56).

Conclusions

We conclude from the current study that breast cancer is a common disease in Iraq and affects groups living in cities and villages. When compared to the control group, the level of chemokine CXCL12 in the blood serum of women with breast cancer increased significantly, a significant increase in the levels of oxidative stress represented by MDA and NO, and a significant decrease in the level of Glutathione in the blood serum of women with breast cancer compared with the control group.

References

1. Cieśla, Sławomir, et al. "The surgical anatomy of the mammary gland (part 1.). General structure, embryogenesis, histology, the nipple-areolar complex, the fascia of the glandular tissue and the chest wall." *Nowotwory. Journal of Oncology* 70.5 (2020): 211-219.
2. Wyld, Lynda, et al., eds. *Breast cancer management for surgeons: a European multidisciplinary textbook*. Cham: Springer International Publishing, 2018.
3. Waldman, Reid A., et al. "Skin diseases of the breast and nipple: benign and malignant tumors." *Journal of the American Academy of Dermatology* 80.6 (2019): 1467-1481.
4. Ebrahim, S. "Knowledge of students toward breast cancer and breast self-examination practice at high school nursing in Basra city." *Rev J Kufa for Nurs Sci* 4.1 (2014): 0-0.
5. Yedjou, Clement G., et al. "Health and racial disparity in breast cancer." *Breast cancer metastasis and drug resistance* (2019): 31-49.
6. Sariego, Jack. "Breast cancer in the young patient." *The American surgeon* 76.12 (2010): 1397-1400.
7. Jemal, Ahmedin, et al. "Cancer statistics, 2010." *CA: a cancer journal for clinicians* 60.5 (2010): 277-300.
8. Zhang ,W.; Li , J. and MC Manus,D.P. (2003).Concept in Immunology and Diagnosis of hydtid disease. *Clin. Microbiol.Rev.* 16(1):18-36.
9. MAHAJAN, SH, and Anita A. Mehta. "Role of cytokines in pathophysiology of asthma." (2006): 1-14.
10. Kumar, Anil, Adeleh Taghi Khani, and Srividya Swaminathan. "Type I interferons: One stone to concurrently kill two birds, viral infections and cancers." *Current Research in Virological Science* 2 (2021): 100014.
11. Vernal, Rolando, and Jose A. Garcia-Sanz. "Th17 and Treg cells, two new lymphocyte subpopulations with a key role in the immune response against infection." *Infectious Disorders-Drug Targets (Formerly Current Drug Targets-Infectious Disorders)* 8.4 (2008): 207-220.
12. Liu, Hui, et al. "Chemokines and chemokine receptors: A new strategy for breast cancer therapy." *Cancer Medicine* 9.11 (2020): 3786-3799.
13. Luther, Sanjiv A., et al. "Differing activities of homeostatic chemokines CCL19, CCL21, and CXCL12 in lymphocyte and dendritic cell recruitment and lymphoid neogenesis." *The Journal of Immunology* 169.1 (2002): 424-433.

14. Kajaria, Divya K., et al. "In vitro antioxidant potential and radical scavenging activity of polyherbal drug Shirishadi." *Oxidants and Antioxidants in Medical Science* 1.3 (2012): 225-229.
15. H Sekhon, Lucky, et al. "Female infertility and antioxidants." *Current Women's Health Reviews* 6.2 (2010): 84-95.
16. Forman, Henry Jay, and Hongqiao Zhang. "Targeting oxidative stress in disease: Promise and limitations of antioxidant therapy." *Nature Reviews Drug Discovery* 20.9 (2021): 689-709.
17. Pimentel, Catarina, et al. "Oxidative stress in Alzheimer's and Parkinson's diseases: insights from the yeast *Saccharomyces cerevisiae*." *Oxidative Medicine and Cellular Longevity* 2012 (2012).
18. Dąbrowska, Emilia, et al. "Possible Diagnostic Application of CXCL12 and CXCR4 as Tumor Markers in Breast Cancer Patients." *Anticancer Research* 40.6 (2020): 3221-3229.
19. Okuyama Kishima, Marina, et al. "Immunohistochemical expression of CXCR4 on breast cancer and its clinical significance." *Analytical Cellular Pathology* 2015 (2015).
20. Mao, Xiao-yun, et al. "MTA1 expression correlates significantly with ER-alpha methylation in breast cancer." *Tumor Biology* 33.5 (2012): 1565-1572.
21. Feng, Lan-Yun, et al. "Involvement of a novel chemokine decoy receptor CCX-CKR in breast cancer growth, metastasis and patient survival." *Clinical Cancer Research* 15.9 (2009): 2962-2970.
22. Wu, Feng-Ying, et al. "Chemokine decoy receptor d6 plays a negative role in human breast cancer." *Molecular Cancer Research* 6.8 (2008): 1276-1288.
23. Müller, Anja, et al. "Involvement of chemokine receptors in breast cancer metastasis." *nature* 410.6824 (2001): 50-56.
24. Xiaowei, Chi, et al. "Overexpression of CXCL12 chemokine up-regulates connexin and integrin expression in mesenchymal stem cells through PI3K/Akt pathway." *Cell Communication & Adhesion* 20.3-4 (2013): 67-72.
25. Faber, Anne, et al. "SDF-1-CXCR4 axis: cell trafficking in the cancer stem cell niche of head and neck squamous cell carcinoma." *Oncology reports* 29.6 (2013): 2325-2331.
26. Darash-Yahana, Merav, et al. "Role of high expression levels of CXCR4 in tumor growth, vascularization, and metastasis." *The FASEB Journal* 18.11 (2004): 1240-1242.
27. Boimel, Pamela J., et al. "Contribution of CXCL12 secretion to invasion of breast cancer cells." *Breast Cancer Research* 14.1 (2012): 1-14.
28. Lilo, Rafal Ahmed, and Rasha Nayyef Ali. "Evaluation of the oxidative state of women with breast cancer in AL-Hilla city." *Basic Education College Magazine For Educational and Humanities Sciences* 48 (2020).
29. Khalaf, Mohammed Yaseen, et al. "The correlation of antioxidant levels of breast cancer: A case controlled study." *Medicine* 100.35 (2021).
30. Nsaif, Ghufra Saad, et al. "Evaluation of Estradiol and Some Antioxidant in Breast Cancer Iraqi Women." *Al-Nahrain Journal of Science* 21.1 (2018): 35-40.
31. Del Rio, Daniele, Amanda J. Stewart, and Nicoletta Pellegrini. "A review of recent studies on malondialdehyde as toxic molecule and biological marker of oxidative stress." *Nutrition, metabolism and cardiovascular diseases* 15.4 (2005): 316-328.

32. Buddi, Rajeev, et al. "Evidence of oxidative stress in human corneal diseases." *Journal of Histochemistry & Cytochemistry* 50.3 (2002): 341-351.
33. Gopal, N., et al. "Serum Gamma GlutamylTransferase levels in Obese South Indian adults with reference to atherogenic lipid risk factors and lipid peroxides." *Int J Med Health Sci* 1.2 (2012): 35-42.
34. Combs Jr, Gerald F., and James P. McClung. *The vitamins: fundamental aspects in nutrition and health*. Academic press, 2016.
35. Khalaf, Mohammed Yaseen, et al. "The correlation of antioxidant levels of breast cancer: A case controlled study." *Medicine* 100.35 (2021).
36. Gönenç, Aymelek, et al. "Plasma malondialdehyde (MDA) levels in breast and lung cancer patients." *Journal of clinical pharmacy and therapeutics* 26.2 (2001): 141-144.
37. Mannaerts, Dominique, et al. "Oxidative stress in healthy pregnancy and preeclampsia is linked to chronic inflammation, iron status and vascular function." *PLoS One* 13.9 (2018): e0202919.
38. Phaniendra, Alugoju, Dinesh Babu Jestadi, and Latha Periyasamy. "Free radicals: properties, sources, targets, and their implication in various diseases." *Indian journal of clinical biochemistry* 30.1 (2015): 11-26.
39. Ahmad, Ashtee Abdulkareem, and Kamaran Abdoulrahman. "the Effect of oxidative stress on tumor suppressor protein p53 and some biochemical markers in breast cancer patients in Erbil governorate." *Zanco Journal of Pure and Applied Sciences* 32.6 (2020): 60-71.
40. Vahora, Huzefa, et al. "The potential role of nitric oxide in halting cancer progression through chemoprevention." *Journal of Cancer Prevention* 21.1 (2016): 1.
41. Fukumura, Dai, Satoshi Kashiwagi, and Rakesh K. Jain. "The role of nitric oxide in tumour progression." *Nature Reviews Cancer* 6.7 (2006): 521-534.
42. Bakshi, A., et al. "The expression of nitric oxide synthases in human brain tumours and peritumoral areas." *Journal of the neurological sciences* 155.2 (1998): 196-203.
43. Fujita, Mayumi, et al. "Role of nitric oxide in pancreatic cancer cells exhibiting the invasive phenotype." *Redox biology* 22 (2019): 101158.
44. Heinecke, Julie L., et al. "Tumor microenvironment-based feed-forward regulation of NOS2 in breast cancer progression." *Proceedings of the National Academy of Sciences* 111.17 (2014): 6323-6328.
45. Ridnour, Lisa A., et al. "Nitric oxide synthase and breast cancer: role of TIMP-1 in NO-mediated Akt activation." (2012): e44081.
46. Desideri, Enrico, Fabio Ciccarone, and Maria Rosa Ciriolo. "Targeting glutathione metabolism: partner in crime in anticancer therapy." *Nutrients* 11.8 (2019): 1926.
47. Yeh, Chih-Ching, et al. "A study of glutathione status in the blood and tissues of patients with breast cancer." *Cell Biochemistry and Function: Cellular biochemistry and its modulation by active agents or disease* 24.6 (2006): 555-559.
48. Kennedy, Luke, et al. "Role of glutathione in cancer: From mechanisms to therapies." *Biomolecules* 10.10 (2020): 1429.
49. Jozefczak, Marijke, et al. "Glutathione is a key player in metal-induced oxidative stress defenses." *International journal of molecular sciences* 13.3 (2012): 3145-3175.

50. Saeed, Mohd, et al. "Virtual screening of natural anti-filarial compounds against glutathione-S-transferase of *Brugia malayi* and *Wuchereria bancrofti*." *Cellular and Molecular Biology* 64.13 (2018): 69-73.
51. Ahmad, Parvaiz, et al. "Drought stress induced oxidative damage and antioxidants in plants." *Oxidative damage to plants*. Academic Press, 2014. 345-367.
52. Ali, Sahib. "Biochemical study on the association of Selenium with hormone of thyroid gland in patients with thyroid disorder." *karbala journal of pharmaceutical sciences* 4.5 (2013): 100-105.
53. Sabour, Aseel Najah, and Zainab Zaidan Mtashar. "Effect of Simvastatin Nanohybrid drug on Liver Tissue and Some of Oxidation Indicators in White Male Rats Induced with Hyperlipidemia." *Scientific Journal of Medical Research* 4.16 (2020): 125-133.
54. Narayanankutty, Arunaksharan, Joice T. Job, and Vinayak Narayanankutty. "Glutathione, an antioxidant tripeptide: dual roles in carcinogenesis and chemoprevention." *Current Protein and Peptide Science* 20.9 (2019): 907-917.
55. Farid, Nevin Mahmoud, Ragaa Reda Hamed, and Abeer Galal Shokeer. "Glutathione and its related enzymes in fasciola snails (*Lymnaea natalensis*): purification and characterization of glutathione transferase." *Research Journal of Agriculture and Biological Sciences* 5.4 (2009): 317-325.
56. Kalpravidh, Ruchaneekorn W., et al. "Glutathione redox system in β -thalassemia/Hb E patients." *The Scientific World Journal* 2013 (2013).