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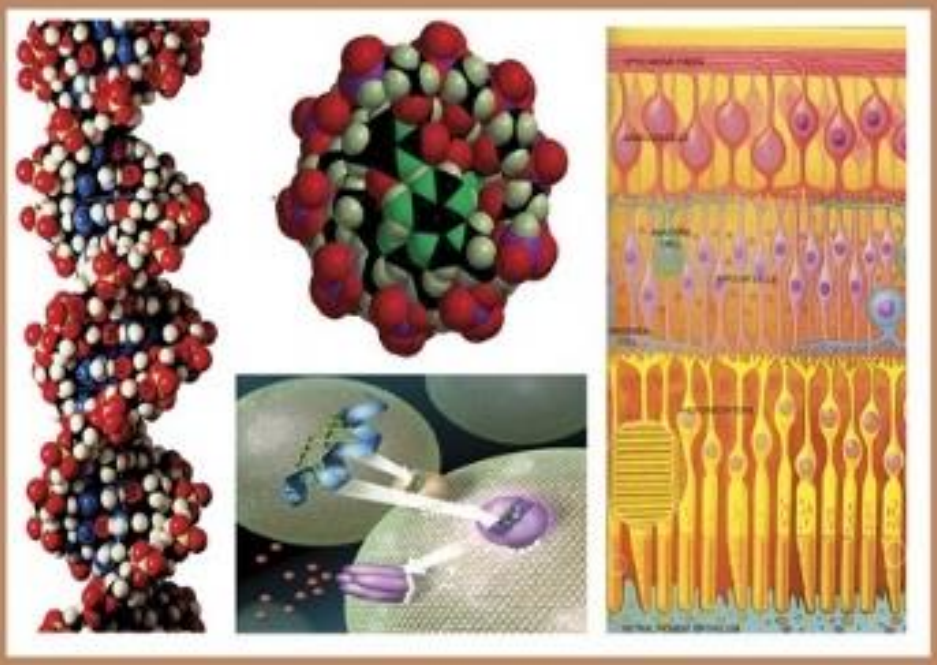

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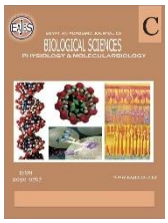

Proline Dehydrogenase As An Indication for Treatment Response in Sera of Patients With Breast Cancer

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ABSTRACT

Breast cancer-BC is a type of cancer that develops in the breast tissue. It is the most common cancer among women worldwide. So the current study aimed to evaluate the activity of serum proline dehydrogenase-PRODH and some biochemical parameters in sera of women with breast cancer as an indication for treatment response. Ninety serum samples were collected from women with and without breast cancer-BC, 30 samples were collected from women with BC(newly diagnosed cases) as the first group-G1 and 30 samples were collected from patients with BC after undergoing chemotherapy as second group-G2. While a 3rd group is a control group C which was collected from 30 healthy women.

The study includes the determination of PRODH, Metaloendopeptidase-MME, Catalase-CAT and Glutathione-S-transferase –GST activity and also the determination of the level of cancer antigen-15-3-CA15-3 and peroxynitrite –PNT in sera of groups under investigation.

The results of the study indicate: In G1 the level of CA15-3 and CAT significantly elevated($P \leq 0.05$), with no significant difference in PRODH, MME, and GST and a significant reduction in the level of PNT as compared with G2 and C, While in G2 the level of PRODH, MME, CAT, and PNT significant difference as a response for treatment, with no significant difference in CA15-3 and GST as compared with G1and C.

We can conclude that the enzymes (PRODH, MME, and GST) may serve as a potential therapeutic target for breast cancer.

INTRODUCTION

Proline dehydrogenase (PRODH) is a mitochondrial enzyme that plays a crucial role in the metabolism of proline(an amino acid residue found in many proteins). (Phang, *et al*., 2015) PRODH catalyzes the oxidation of proline to pyrroline-5-carboxylate, which can then be further metabolized to produce energy or used in other metabolic pathways. (Liu, *et al*.,2009) PRODH has been implicated in a variety of physiological processes, including cell growth and differentiation, oxidative stress response, and apoptosis (Natarajan, *et al*.,2020). Dysregulation of PRODH expression or activity has been linked to several diseases, including cancer(Ghasemvand, *et al*.,2015), schizophrenia, and neurodegenerative disorders. (Liu, *et al*.,2020).

Recent studies have also suggested that PRODH may play a role in regulating immune responses and inflammation, and also in cancer development and progression, including breast cancer (Fang, *et al*., 2015; Cherra, *et al*.,2008).

Studies have shown that PRODH expression is down regulated in breast cancer tissues compared to normal tissues, and its decreased expression is associated with poor prognosis and increased metastasis (Fang, *et al*.,2019). Additionally, PRODH has been shown to induce apoptosis and inhibit cell proliferation in breast cancer cells, suggesting its potential as a therapeutic target. However, further research is needed to fully understand the role of PRODH in breast cancer(Natarajan, *et al.*,2012; Phang, *et al*., 2015; Fang, *et al*.,2019). So the current study aimed to evaluate the activity of serum proline dehydrogenase and some biochemical parameters in sera of women with breast cancer as an indication for treatment response.

MATERIALS AND METHODS

Study Design: 90 serum samples were collected from women with and without breast cancer-BC.Thirty samples were collected from patients women with BC(newly diagnosed cases) as the first group-G1 and thirty serum samples were collected from patients with BC after undergoing chemotherapy as second group-G2. While a 3rd group is a control group C which was collected from 30 healthy women.

The ages range for the three groups is between 30-71 years. The samples were collected from Oncology teaching hospital-Bagdad and Tikrit general hospital from the period between 1/11/2021 to 1/3/2022.

Methods: The activity of enzymes (PRODH, Metaloendopeptidase-MME, Catalase and Glutathione-S-transferase) were determined in sera of patients and control groups by using The enzyme-linked immunosorbent assay-ELISA for PRODH and spectrophotometric methods for other enzymes (Habig, *et al*.1974; Abi, *et al*.1974), and the study also include determining the level of Cancer antigen-15-3-CA15-3 and peroxynitrite - PNT(Duffy, *et al*.1999,12; Vanuffelen, *et al*.2001).

Statistical Analysis: The data obtained were subjected to statistical analysis using Duncan's Multiple Range tests with the SPSS program, at a probability level of $p \leq 0.05$.

RESULTS

The study includes the determination of some biochemical parameters in sera of patients with breast cancer,(which is divided into two groups G1- newly diagnosed cases with BC and G2- patients with BC after undergoing chemotherapy) and a control group. The results of obtaining from the study were summarized in Table 1.

Table 1: The Mean ±SD of parameters under investigation in sera of patients with BC and control groups.

Parameters	Control group	First group	Second group
CA15-3(U/ml)	2.623±0.967b	23.473±3.731 a	6.449±2.825 b
PRODH (ngm)	262.026±33.183 b	271.456±41.135b	301.135±36.817a
MME (U/ml)	16.242±4.105b	17.739±5.668ab	18.923±3.222a
CAT(K/ml)	0.286±0.152c	0.716±0.196b	1.257±0.269a
GST(U/L)	3.541±1.033ab	4.315±0.844a	2.618±0.393b
)mol/L (µPNT	46.027±12.440b	24.675±7.951c	59.393±11.545a

Levels of CA15-3, PRODH and MME:

Table 1 showed that the level of CA15-3 significantly elevated($P \leq 0.05$) in G1 as compared with G2 and C, Figure 1. While the activity of PRODH and MME significantly elevated ($P \leq 0.05$) in G2 as compared with G1 and C, Figure 2, Gig3.

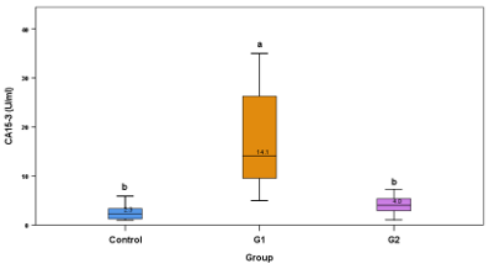

Fig. 1: CA15-3 level in sera of patients and control

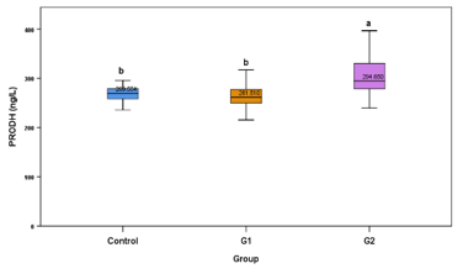

Fig. 2: PRODH activity in sera of patients and control

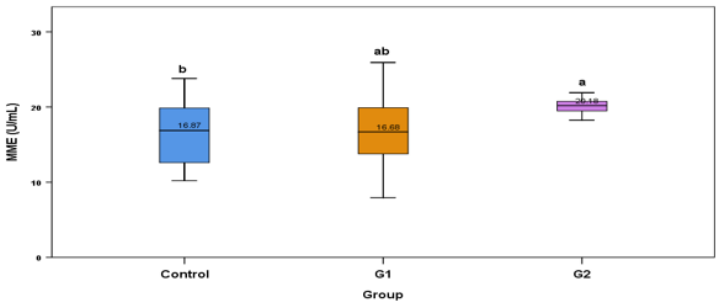

Fig.3: MME activity in sera of patients and control groups

Levels CAT, GST and PNT:

The results also indicate that the activity of CAT significantly elevated in the patients' group (especially in G2) as compared with the control group, Figure 4. No significant difference between the patients' group as compared with C for GST activity, with significant elevated in G1(newly diagnosed cases) as compared with G2, Figure 5. While the level of PNT showed a significant reduction in G1 and significantly elevated in G2 as compared with the control group, Figure 6.

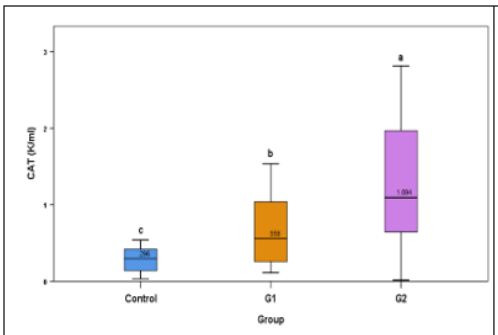

Fig. 4: CAT activity in sera of patients and control groups

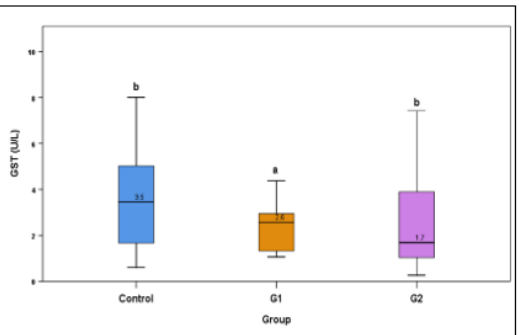

Fig. 5: GST activity in sera of patients and control groups

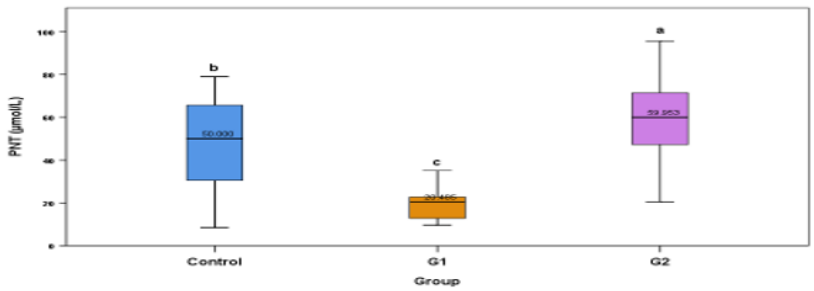

Fig. 6: PNT level in sera of patients and control group

DISCUSSION

Breast cancer is one of the most common types of cancer among women worldwide. The early detection and diagnosis of breast cancer are crucial for successful treatment and improved patient outcomes. Cancer antigen 15-3 (CA 15-3) is a tumor marker that has been extensively studied in breast cancer patients. CA 15-3 is a glycoprotein that is expressed on the surface of breast cancer cells and released into the bloodstream. Elevated levels of CA 15-3 have been associated with advanced stages of breast cancer, metastasis, and poor prognosis. However, CA 15-3 is not specific to breast cancer and can also be elevated in other malignancies and non-cancerous conditions. Therefore, the use of CA 15-3 as a diagnostic tool for breast cancer should be interpreted in conjunction with other clinical and radiological findings. Nonetheless, monitoring changes in CA 15-3 levels during treatment can provide valuable information on disease progression and response to therapy (Duffy, *et al*. 2010; Li, *et al*.2018).

The current study aimed to evaluate the activity of PRODH in sera of patients with BC, Recent studies have shown that PRODH expression is altered in breast cancer, with decreased expression observed in some cases and increased expression in others. In triple-negative breast cancer (TNBC), PRODH is downregulated, leading to increased proline levels and promoting tumor growth and metastasis. On the other hand, in estrogen receptor-positive (ER+) breast cancer, PRODH overexpression has been associated with poor prognosis and resistance to endocrine therapy. These findings suggest that PRODH may serve as a potential therapeutic target for breast cancer treatment. Further research is needed to fully understand the role of PRODH in breast cancer and its potential as a therapeutic target (Liu, *et al*. 2009; Fang, *et al* .2019)The results of the current study indicate that the activity of PRODH significantly elevated after treatment with chemotherapy, that is may be due to the crucial role of the enzyme in inhibiting tumor growth and blocking the cell cycle by the production of ATP or inducing reactive oxygen species autophagy (Liu, *et al*. 2021). Metalloendopeptidases are a class of enzymes that play a crucial role in the regulation of various physiological processes, including cell growth, differentiation, and apoptosis. Recent studies have shown that metalloendopeptidases are involved in the development and progression of breast cancer. Specifically, metalloendopeptidase ADAM17 has been found to promote breast cancer cell proliferation and invasion by cleaving various growth factors and cytokines. In contrast, metalloendopeptidase ADAM10 has been shown to inhibit breast cancer cell migration and invasion by cleaving E-cadherin. These findings suggest that metalloendopeptidases may serve as potential therapeutic targets for the treatment of breast cancer(Li, *et al*. 018; Li, *et al*. 2019)

Catalase is an enzyme that plays a crucial role in the metabolism of hydrogen peroxide, which is a reactive oxygen species (ROS) that can cause oxidative damage to cells. Recent studies have suggested that catalase may also play a role in breast cancer. One study found that low levels of catalase expression were associated with poor prognosis in breast cancer patients (Kim, *et al*. 2014). Another study found that overexpression of catalase inhibited the growth and invasion of breast cancer cells(Wang, *et al*.2016). These findings suggest that catalase may be a potential therapeutic target for breast cancer treatment.

Glutathione-S-transferase is an enzyme that plays an important role in the detoxification of xenobiotics and endogenous compounds. Several studies have reported the association between GST polymorphisms and breast cancer risk (Wang, *et al*.2010). The GSTM1 null genotype has been found to be associated with an increased risk of breast cancer in some populations, while the GSTT1 null genotype has been associated with a decreased risk (Kocabas, *et al*.2005). Additionally, GSTP1 polymorphisms have also been linked to breast cancer

susceptibility. Furthermore, GST expression levels have been shown to be altered in breast cancer tissues compared to normal tissues, suggesting a potential role in breast cancer development and progression. Overall, these findings suggest that GST may play a significant role in breast cancer pathogenesis and may serve as a potential therapeutic target for this disease(Hayes, *et al*.2005; Singh, *et al*,2010; Wang, *et al*.2010).

Peroxynitrite is a reactive nitrogen species that have been implicated in the development and progression of breast cancer. Studies have shown that peroxynitrite can induce DNA damage, activate oncogenic signaling pathways, and promote tumor growth and metastasis. In addition, peroxynitrite is elevated in breast cancer tissues compared to normal tissues, suggesting a potential role in the pathogenesis of the disease. Several studies have also investigated the use of peroxynitrite inhibitors as a potential therapeutic strategy for breast cancer. For example, one study found that treatment with a peroxynitrite scavenger reduced tumor growth and metastasis in a mouse model of breast cancer (Liu, *et al*. 2015). Another study showed that inhibition of peroxynitrite production using an antioxidant compound reduced cell proliferation and induced apoptosis in breast cancer cells (Gao, *et al*.2017). Overall, these findings suggest that targeting peroxynitrite may be a promising approach for the treatment of breast cancer.

Conclusion:

From the results of the present study, we can conclude that the enzymes (PRODH, MME and GST) and may serve as a potential therapeutic target for breast cancer.

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