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Review

Are antioxidant enzymes essential markers in the diagnosis and monitoring of cancer patients – A review

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ABSTRACT

Reactive oxygen species (ROS) play a significant role in human cells. Excessive ROS production damages important macromolecules such as nucleic acids and can initiate and develop the carcinogenesis process. Antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione reductase (GR), glutathione peroxidase (GPx), and xanthine oxidoreductase (XOR) are responsible for maintaining the balance between the functions of free radical formation and eliminating their excessive amounts.

Based on the analyzed literature, the following conclusions can be made:

1. Antioxidant enzymes activity are important for diagnosing neoplastic diseases such as non-small-cell lung cancer, bladder cancer, ovarian cancer, and colon cancer.

2. Non-small-cell lung cancer is usually characterized by decreased SOD and CAT activity and increased glutathione GST activity. Lowered SOD, CAT, and GPx activity is characteristic of bladder cancer. XOR, CAT, SOD and GPx expression is decreased in patients with ovarian cancer. Colorectal cancer is characterized by increased MnSOD expression (*in vitro* studies) and SOD expression while CAT, GPx, and GR are decreased (*in vivo* study).

3. SOD, CAT, and XOR are promising prognostic markers in cancer of the lung, bladder, ovarian, and colon.

1. Introduction

Human body cells in homeostasis produce small amounts of reactive oxygen species (ROS). ROS participates in many cellular processes by activating signaling pathways essential for normal cell growth and proliferation. Excessive ROS production may cause damage to important macromolecules – nucleic acids, proteins, and lipids. However, cells present many substances that can remove the molecules responsible for causing damage. The most important of these substances are antioxidant enzymes, including superoxide dismutases (SOD), glutathione peroxidases (GPx), catalase (CAT), xanthine oxidoreductase (XOR), and glutathione reductase (GR). Although the antioxidants are present in various structural forms and extracellular and intracellular spaces, their function produces a coherent antioxidant protection system. Understanding the activity and concentration levels of antioxidant enzymes allows for assessment of the global risk of developing selected diseases based on the excessive formation of free radicals and ROS [1,2,3] Fig. 1 Table 1 Table 2 Table 3 Table 4.

2. Antioxidant enzymes

Superoxide dismutases (E.C. 1.15.1.1.) are the first line of defense against ROS. Superoxide dismutases are metalloenzymes. In their active centers are metal ions with different valances. There are three isoforms of SOD depending on the metal cofactor: cytoplasmic, extracellular, and mitochondrial SOD [2,3].

SOD catalyzes the reaction of dismutation of superoxide (O2–) to hydrogen peroxide and molecular oxygen in a two-step process. The first step is reducing the metal ion with the simultaneous oxygen molecule release. The second step consists of oxidation of the metal ion; it happens with the superoxide radical ion and oxygen participation. At the same time, H_2O_2 is produced [2,3].

The superoxide anion is formed only in the presence of oxygen. Dismutases protect the cells against the cytotoxic effects of this

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compound [2,3].

Catalase (EC 1.11.1.6) is an enzyme also involved in reactions that neutralize ROS. Catalase is responsible for the dismutation of hydrogen peroxide. This process takes place in two stages. [2,4].

- reaction 1: H_2O_2 + Fe(III)-CAT → $2H_2O$ + O + Fe(V)-CAT
- reaction 2: H_2O_2 + O = Fe(V)-CAT → Fe(III)-CAT + H_2O + O_2

When the H_2O_2 concentration is high, catalase unfolds hydrogen peroxide into oxygen and water. However, GPx has a greater affinity to H_2O_2 than catalase. Therefore, it plays a more important role in physiological situations where the amounts of generated hydrogen peroxide are not large. The lack of catalase is compensated by increased peroxidase activity and vice versa. Catalase exhibits peroxidase activity at low hydrogen peroxide concentrations [2,4].

Glutathione peroxidases (EC 1.11.1.9) constitute the first and second line of defense against ROS. They reduce H_2O_2 and organic peroxides with the help of reduced glutathione. GPx is responsible for the oxidation of glutathione. At the same time, it does not produce the free GSH thiol radical. This occurs due to the presence of selenocysteine in the active center of this enzyme. [2,3,4].

Glutathione S-transferases (EC 2.5.1.18) constitute a family of three proteins: microsomal, cytosolic, and mitochondrial forms. Glutathione S-transferases participate in the second phase of xenobiotic detoxification and remove oxidized GSH, formed as a product of H_2O_2 reduction, with the participation of glutathione, which donates the protons outside the cell. Glutathione S-transferase is also responsible for the inactivation of endogenous unsaturated aldehydes, peroxides, and epoxides. These compounds are the reactive products of oxidative stress [2,3,4].

Glutathione reductase (GR) is an enzyme related to glutathione and is found in the mitochondria and cytosol. GR is responsible for maintaining proper GSH concentrations by converting GSSH into glutathione. Glutathione reductase also participates in reactions responsible for oxygen detoxification [2,3,4].

Xanthine oxidoreductase (XOR) is a homodimeric metalloflavoprotein. [5,6]. XOR works to catalyze the oxidation of hypoxanthine to xanthine and xanthine to uric acid, the last two steps of purine catabolism in the highest uricotelic primates (Fig. 2). XOR exists in two interconverting alternative isoforms, xanthine dehydrogenase and xanthine oxidase, which play a significant role in cells and tissues during injury. Both isoforms have opposing effects – xanthine dehydrogenase has antioxidant effects, while xanthine oxidase has pro-oxidative effects [5,6].

3. Lung cancer

Over the past 100 years, lung cancer has become one of the most common cancers with over one and a half million deaths each year. Lung cancer usually originates from epithelial cells. Clinically, there are two types of lung cancer: non-small-cell and small-cell, which constitute approximately 85% and 15% of lung cancers, respectively [1,7,8].

Lungs are directly exposed to high oxygen pressure. Additionally, they are exposed to the adverse effects of smoking and harmful effects of car exhaust fumes and industrial pollution, which are present in the form of fine dust. All these factors are responsible for the generation of free radicals that can cause the formation of oxidative stress in the lungs and other organs [1,7].

Table 1
Antioxidant enzymes as biomarkers in lung cancer.

Parameters	Importance	Research	References
low MnSOD activity, low Cu/ZnSOD activity low CAT activity; GSH increased GSH activity and related enzymes – GPx, GST, GR – was significantly higher in cancer tissues than in adjacent noncancerous tissues in patients with adenocarcinoma and squamous cell carcinoma	Protects lung cells from oxidative stress	Zalewska-Ziob et.al 2019	[1]
increase SOD and decrease CAT activity in tumor tissue than in adjacent non-cancerous tissues of non-small-cell lung carcinoma	Promotion of cancer	Chung-mang et al.2001	[9]
increase SOD and CAT, GST, GSH activity in tumor tissue than in control group;	Protects lung cells from oxidative stress	Kaynar et al. 2005	[10]
high SOD activity levels	implications in lung cancer monitoring and as a predictor of outcome	Carpagnano et al. 2012	[11]
large amounts of GSH, compared to a healthy lung	Protective for patients with lung cancer	Luengo et al.2019	[12]
decreased GSH levels compared to a healthy lung		Tang et al. 2010	[13]
increased expression of XOR	worse prognosis for patients with NSCLC who received adjuvant chemotherapy	Kim et al. 2012	[14]
high tumoral XOR expression with adenocarcinoma	predictor of a poor prognosis in patients with adenocarcinoma of the lung	Konno et al. 2012	[15]

The lungs are protected against the harmful effects of free radicals by antioxidant enzymes such as SOD, GST, GPx, GSH, or CAT. However, disturbances in the action of these antioxidants can lead to metabolic disorders and, consequently, cell death [1].

Zalewska-Ziob et al. carried out a study in which the activity of selected antioxidant enzymes in tumor tissues and adjacent noncancerous tissue was determined. These studies included 53 patients aged 47 to 75 years diagnosed with non-small-cell lung cancer [1]. A significant change in antioxidant enzyme activity in the carcinogenesis process was observed. As compared to healthy tissue, cancer cells have always exhibited low MnSOD activity, typically low Cu/ZnSOD activity, and almost always have low catalase activity. GSH-related enzyme activity significantly increased in lung cancer tissues irrespective of the

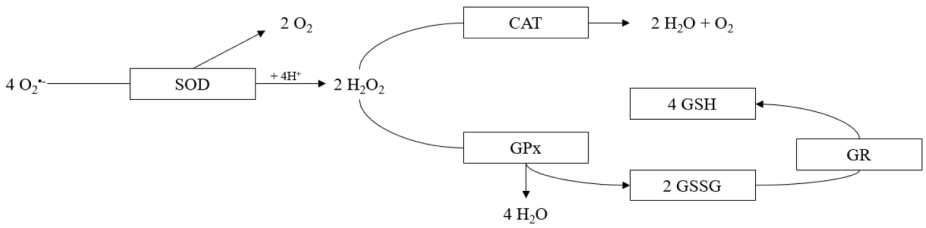

Fig. 1. Participation of SOD, CAT, GPx and GR in the neutralization of free radicals [2,3,4].

Table 2
Antioxidant enzymes as biomarkers in bladder cancer.

Parameters	Importance	Research	References
lower levels of SOD, CAT activity in patients suffering from bladder cancer compared to patients with benign tumors/ healthy tissues. Increased CAT activity with the stage of cancer	Diagnosis of cancer, prognostic biomarker	Islam et al 2018 ; Duran et al 1997.; Jeon et al 2007	[17,18,19]
decreased SOD, GSH, GPx activity	Diagnosis of cancer	Gecit et al.2017	[20]
increased activity of Mn-SOD in bladder cancer causes a 3-fold increase in the invasiveness of this tumor.	monitoring the patient's condition and telling whether the tumor is going into an invasive phase	Connor et al. 2007	[21]
decreased glutathione peroxidase activity in patients with bladder cancer compared to non-cancer patients	Diagnosis of cancer	Arikan et al. 205	[22]
decreased activity of enzymes XOR, SOD, GPx, and CAT in patients with bladder cancer	severe exposure of cancerous tissues to oxidative stress	Bayraktar et al.2010	[24]
decreased GPx activity	–	Wieczorek et al. 2017	[23]

Table 3
Antioxidant enzymes as biomarkers in ovarian cancer.

Parameters	Importance	Research	References
increased expression of XOR	prognostic factor; increases the probability of death of patients	Linder et al. 2012	[25]
lower CAT activity relative to the control group; Lower CAT activity in stage III and IV of the disease	poor prognostic index for female patients, indicating tumor advancement the severity of peroxidation	Didžiapetrienė et el. 2014; Manimaran et al. 2009 Senthil et al. 2004	[26,28,29]
decreased SOD and GPX activity and increased MDA levels in patients with epithelial ovarian cancer	indicating tumor advancement	Ramadan et al. 2017	[30]
decreased CAT and SOD activity and increased GPx activity in ovarian tumor biopsy tissue compared to normal tissue; GSH, MDA levels increased	shift of oxidative metabolisms towards a pro-oxidation state and potential gene instability in malignant ovary cells	Sanchez et al. 2006 Senthil et al. 2004	[29,31]
decreased activity CAT and SOD in platelets	strong oxidative stress	Gorozhanskaia et al 2003	[32]

histological type of lung cancer, which may be how cancer cells protect themselves from increased oxidative stress [1].

Superoxide dismutases play a major role in protecting the lungs from the free radicals produced by properly functioning metabolism. SOD is responsible for preventing the formation of oxidative stress in the lungs

Table 4
Antioxidant enzymes as biomarkers in colorectal cancer.

Parameters	Importance	Research	References
decreased expression of MnSOD	expression was significantly higher in the advanced stages of tumors with a high degree of mitochondrial DNA microsatellite instability	Govati et al. 2016 Janssen et al. 1999 Toh et al. 2000	[35,36,37]
Increased of SOD activity and decreased of CAT, GPx and GR activity	Potential diagnostic indicators of CRC advancement.	Zińczuk et al. 2019	[38]
increase in the activity of XOR, CAT, SOD, NADPH oxidase, and the level of TAC; relationship between CAT activity and the intensity of the inflammatory tumor infiltration	biomarkers useful for the evaluation of tumor progression	Zińczuk et al. 2020 Malinowska et al. 2015 Czeczot et al. 2005 Farias et al. 2011	[39,40,41,42]
increased expression of GST	poor prognosis in patients with colorectal cancer	Gulubova et al. 2010	[44]
decreased of CAT activity	prognostic marker in the treatment of colorectal cancer	Marjaneh et al 2018	[45]
increased CAT activity and decreased SOD in patients with colorectal cancer compared to people with intestinal polyps and in the control group	Predictive biomarkers of CRC cancer risk	Maffei et al. 2011	[46]
increased in SOD and TAS activity/levels in colon tumors compared to normal colon tissue in stages I-III and a decrease in stage IV, respectively	biomarkers useful for the evaluation of tumor progression	Kocot et al. 2013	[47]
zinc supplementation during chemotherapy cycles increased SOD activity and maintained vitamin E concentration	a positive effect on cancer treatment	Ribeiro el al.2016	[48]

[1]. This explains how antioxidant enzymes can provide important information about oncological processes. However, *Chung-man Ho et al.* reported different results. The researchers studied antioxidant expression in 16 lung tumors and 21 tumor-free lung tissues collected from 24 individuals with surgically resectable non-small cell lung cancer, i.e., adenocarcinoma and squamous cell carcinoma. They showed that total SOD activity was increased, CAT activity decreased, and GSH and GPx were similar in tumors compared with tumor-free lung tissues. Immunohistochemical localization of catalase in the lung revealed been reduced or no expression in the tumor cells, although healthy adjacent airway epithelial cells were strongly positive for catalase. The authors argue that inflammation in the lung may contribute to high levels of manganese SOD and decreased CAT, which together may lead to increased hydrogen peroxide intracellularly and create an intracellular environment favorable to DNA damage and the promotion of cancer [9]. Similar results were presented in 2005 by *Kaynar et al.* They demonstrated increased SOD activity in the erythrocytes of patients who have

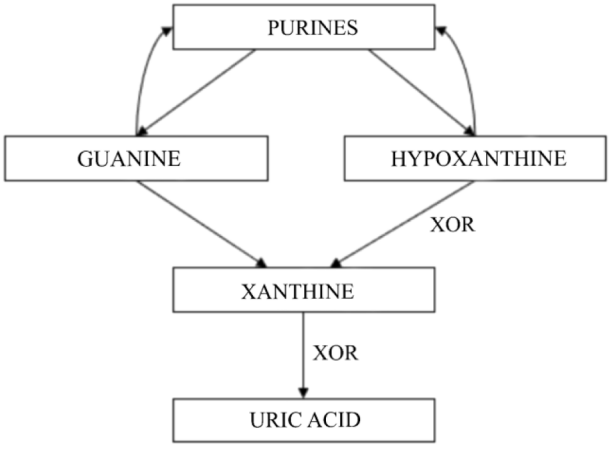

Fig. 2. The role of xanthine oxidoreductase (XOR) in two last stages of purine catabolism, catalysis of xanthine and uric acid formation [5,6].

non-small-cell lung cancer compared with a healthy control group [10]. Considering the beneficial effects of SOD in the lungs, these results may show a better prognosis of patients participating in this study.

The study of SOD activity and ferritin levels in exhaled air condensate (EBC) seems very interesting. *Carpagnano et al.* Conducted a study to check the predictive power of these markers. Forty patients with non-small cell lung cancer (NSCLC) and 15 controls were enrolled in the study. All subjects under study underwent EBC collection and analysis of ferritin and SOD. A total of 36 patients were either given a follow-up of at least 25.5 months or followed up until death. This study demonstrated that exhaled ferritin and SOD resulted in higher NSCLC than in controls and influenced by the stage of cancer. Thus, we can hypothesize that the concept of measuring ferritin and SOD in EBC may have clinical implications in lung cancer monitoring and as a predictor of outcome. These results are promising, but the authors indicate the need to expand the study group [11].

Body aging is associated with the formation of oxidative stress in the cells, caused by the accumulation of damage in DNA, proteins, and lipids. *Zalewska-Ziob et al.* compared antioxidant enzyme activity in patients with NSCLC, dividing them into two groups – under and over 65 years of age. However, no differences were observed in the activity of the three superoxide dismutase isoforms in neoplastic and non-neoplastic tissues in either group. There was no significant difference in the SOD activity between women and men [1].

A significant reduction in catalase activity has been observed in many types of cancer: head and neck, gastrointestinal, lung, breast, and kidney cancer. One study showed that CAT activity in non-small-cell lung cancer was significantly increased in adjacent noncancerous tissues compared to cancer tissues [1].

The study conducted in 2001 by *Chungman et al.* showed reduced catalase activity in cancer tissues compared to healthy tissues around the tumor [9]. On the other hand, *Kaynar et al.* demonstrated increased CAT activity in the erythrocytes of NSCLC patients as compared to the healthy control group [9].

It is believed that glutathione and other associated enzymes are the primary mechanisms of lung protection against free radicals. GSH protects against oxidative stress by reducing hydroperoxides, suppressing the action of free radicals, and detoxifying xenobiotics. The GSH-dependent antioxidant system consists of glutathione and its associated enzymes. They include glutathione S-transferase, glutathione peroxidase, and glutathione reductase [1].

Zalewska-Ziob et al. showed that GSH activity and related enzymes – GPx, GST, GR – was significantly higher in cancer tissues than in adjacent noncancerous tissues in patients with adenocarcinoma and squamous cell carcinoma. However, the activity of these enzymes was not significantly different between the two histological types of NSCLC [1].

The experiment conducted by *Kaynar et al.* showed slightly increased GSH and GST activity compared to control samples [10]. Also, Luengo et al. Show that NSCLC accumulates huge amounts of GSH, compared to a healthy lung, necessary for methylglyoxal detoxification. Derived products (AGEs) can inhibit lung tumor growth. This study shows that GSH is very protective for patients with lung cancer [12]. On the other hand, the *Tang et al.* study demonstrated lowered GST expression in tumor tissues compared to adjacent noncancerous tissues [13].

Glutathione is necessary for an effective immune response by activating T cells and polymorphonuclear leukocytes to produce cytokines. Therefore, there may be a correlation between GSH-related enzymes and tumor formation. Mediators and cellular inflammatory factors are important components of neoplastic tissue. As a result, cancer cells protect themselves by increasing intracellular GSH concentrations. Inflammation around the tumor promotes the proliferation and survival of malignant cells, promotes angiogenesis and metastasis, while also altering the immune response as well as the response to hormones and chemotherapeutic agents [1].

Diksha et al. study investigated whether GSH and inflammatory markers could be markers of response to chemotherapy in NSCLC. However, no such relationship was shown, except for Il-6 [14].

A very interesting enzyme in monitoring survival in lung cancer patients is XOR. *Kim et al.* showed that Low XOR expression was associated with shortened survival and conferred a worse prognosis for patients with NSCLC who received adjuvant chemotherapy [15]. However, *Konno et al.* showed that high tumoral XOR expression is an independent predictor of a poor prognosis in patients with adenocarcinoma of the lung [16]. These results indicate that the importance of XOR as a prognostic factor for patient survival depends on the type of tumor. However, more research is needed to answer this question unambiguously.

4. Bladder cancer

Bladder cancer is the most common malignant neoplasm of the urinary system. It is characterized by high aggressiveness and a poor prognosis. Transient urothelial bladder tumors are classified as non-muscle invasive (NMI) (pTa or pT1) or invasive (pT2, pT3, or pT4) with a worse prognosis [17].

The trivalent inorganic, arsenic, inhibits cellular enzymes by binding to the sulfhydryl groups dihydrolipoamide which reduces cellular ATP production. Furthermore, trivalent arsenic inhibits the production of glutathione which protects cells against reactive oxygen species. Tobacco smoke contains many carcinogens such as polycyclic aromatic hydrocarbons. Smoking cigarettes increases the formation of ROS [17].

In 2018, *Islam et al.* conducted studies showing different activity and expression of antioxidants enzymes, including superoxide dismutase, catalase or glutathione peroxidase, in bladder cancer [17]. SOD has a protective effect on different types of tissues, protecting them against negative effects of oxidative stress. The study showed lower levels of superoxide dismutase activity in patients suffering from bladder cancer compared to patients with benign tumors. SOD expression was significantly lower in the transitional invasive cancer cells than in surface tumor cells. Changes in SOD activity have also been demonstrated in serum isolated from bladder cancer patients [17]. Additionally, studies conducted by *Duran et al.* and *Jeon et al.* found reduced SOD activity in neoplastic tissues in comparison with healthy tissues [18,19].

Similar results were obtained by Gecit et al. They showed that in patients with bladder tumors, oxidants (MDA, NO, prolidase) had higher levels, and antioxidants (SOD, GSH, GPx) were less active than in bladder cancer patients. They also established that ROS plays a role in bladder cancer's etiology, like many other cancers and inflammation, while assuming that antioxidants may be beneficial in preventing and treating bladder cancer [20].

Connor et al. Showed that the increased activity of Mn-SOD in bladder cancer causes a 3-fold increase in the invasiveness of this tumor.

This indicates the enormous importance of this enzyme as a potential diagnostic marker and monitoring the patient's condition and telling whether the tumor is going into an invasive phase [21]. *Islam et al.* demonstrated decreased activity and expression of CAT in bladder neoplastic tissues compared to non-cancerous control tissues [16]. *Durak et al.* demonstrated analogous results, moreover, they found that CAT activity increased with tumor advancement [16]. Decreased catalase activity in bladder cancer tissue was also confirmed by the results obtained by *Jeon et al.* Catalase expression was significantly lower in invasive transient cancer cells than in superficial transient neoplastic cells [18].

GSH and its related enzymes – glutathione S-transferase, glutathione peroxidase and glutathione reductase – play a significant role in preventing disease formation, including cancer. In *Islam et al.,* lower glutathione peroxidase activity was observed in red blood cells and bladder cancer tissues when compared to bladder tissues in patients without tumors and those with benign tumors. It was found that decreased glutathione activity may contribute to the transition from the intracellular environment to the pro-oxidative state, which leads to the occurrence of many changes in the body [16].

Glutathione, which plays a significant role as an intracellular antioxidant, is also involved in many metabolic processes. GSH and its related enzymes – glutathione S-transferase, glutathione peroxidase, and glutathione reductase – play a significant role in preventing the formation of many diseases, including cancer. *Islam et al.* reported lower glutathione peroxidase activity in red blood cells and bladder cancer tissues compared to bladder tissues in patients either without tumors or those with benign tumors. They found that the decrease in glutathione activity may contribute to the transition from the intracellular environment to the pro-oxidative state, leading to the occurrence of many changes in the body [16].

These results were confirmed by studies carried out by *Arikan et al.,* who also found decreased glutathione peroxidase activity in patients with bladder cancer compared to non-cancer patients [22]. On the other hand, *Wieczorek et al.* noted significantly increased GPx activity in patients with bladder cancer compared to healthy patients [23].

The results analogous to those presented above were obtained by *Bayraktar et al.* They showed a decrease in the activity of enzymes XOR, SOD, GPx, and CAT in patients with bladder cancer, which was associated with a severe exposure of cancerous tissues to oxidative stress [24].

The results described above show that the activity of antioxidant enzymes is decreased in patients with bladder cancer. SOD and CAT seem to be essential biomarker that could diagnose and monitor the patient's condition.

5. Ovarian cancer

Ovarian cancer has the highest mortality rate among gynecological neoplasms. It includes several histological types with a different survival profile for each. It is estimated that the global incidence rate for ovarian cancer is six in 100,000 women, with a mortality rate of four in 100,000. The average European survival rate is approximately 40%, and survival primarily depends on disease stage. Patients in stage I show a favorable survival rate of around 90%, while patients in stage IV have a survival rate of 12–18%. The most common subtype of epithelial ovarian cancer is sera which accounts for approximately 50–60% of all ovarian cancer cases [25,26].

Lysophosphatidic acid is gaining in importance as potential ovarian cancer biomarkers, which can be used both for diagnosis and, above all, to monitor patients' condition. Especially in the latter case, it may be a more sensitive marker than Ca125. Antioxidant enzymes are also gaining importance as biomarkers in ovarian cancer [27].

The risk factors for ovarian cancer include the absence of pregnancies, endometriosis, a history of cancer, obesity, hyperestrogenism, and genetic factors such as mutations in the BRCA1 or BRCA2 genes [28,29]. In 2011, *Linder et al.* assessed xanthine oxidoreductase activity in ovarian cancer. The study involved 522 patients treated for serous ovarian cancer. They collected tumor samples during surgery prior to chemotherapy [25]. Despite XOR's biochemical function, which is to maintain the cell's proper state during purine catabolism, its activity is also regulated by many other factors. Hypoxia activates XOR both at the transcriptional and post-transcriptional levels [29].

The study showed xanthine oxidoreductase expression reduced 64% of serous ovarian cancer tumors than the healthy human epithelium of this tissue. The predictive value of XOR showed patients who did not express this enzyme had an approximately two-fold high risk of death from ovarian cancer compared with patients who had high xanthine oxidoreductase activity. It has been shown that patients with (who had small, residual tumors shorter than 1 cm or tumor smaller than 10 cm, whose tumor showed low proliferation index or regular expression of p53 protein) had a worse prognosis loss of XOR activity [25].

In 2014, Didziapetriene et al. assessed catalase activity in ovarian cancer patients. The study involved 42 newly diagnosed women, aged 22 to 67 years. These women were divided according to cancer stage [26]. Catalase activity was assessed in four disease stages to determine if CAT could be a prognostic survival marker in ovarian cancer patients. Ovarian cancer patients showed significantly lower catalase activity compared to the healthy control group. CAT activity was slightly higher in patients with stage I and II than in stage III and IV patients. There was no significant difference in age-dependent survival. It was also reported that oxidative stress is present in neoplastic cells and other cells of patients who have cancer [26].

Manimaran et al. also observed low catalase activity in patients with ovarian cancer. The decrease in catalase activity could be due to an increase in malondialdehyde, a product of lipid peroxidation. The malonic aldehyde can form cross-links, thereby inactivating membrane-bound enzymes. Decreased CAT activity may also be caused by enzyme depletion due to increased peroxidation [28]. These results were also confirmed by the studies carried out by Senthil et al. in which they showed significantly lower catalase activity in ovarian cancer tissue compared to healthy tissues [29].

Ramadaan et al. investigated SOD, GPx, and MDA (Malondialdehyde) activity in women with epithelial ovarian cancer and benign ovarian tumors as compared to controls. They showed that patients with epithelial ovarian cancer (EOC) had decreased preoperative serum levels of SOD and GPX antioxidants and increased MDA levels. These findings were associated with advanced tumor stage. The study confirmed the role of oxidative stress in the development of epithelial ovarian cancer [30].

In another study conducted on a group of women with advanced epithelial ovarian cancer (EOC), decreased CAT and SOD activity and increased GPx activity was found in ovarian tumor biopsy tissue compared to normal tissue. These results are in line with the current knowledge of antioxidant enzymes. Glutathione peroxidase has a greater affinity than catalase for hydrogen peroxide in non-physiological situations. This explains the decreased activity of CAT and the increased activity of GPx in ovarian cancer [4]. Moreover, they found that the levels of GSH increased, giving; as a result, a reduction of the oxidative stress marker GSSG / GSH ratio comparing normal ovarian tissue with tumor tissue. Besides, the oxidation products MDA and 8-oxo-dG (8-Hydroxy-2′-deoxyguanosine) are significantly increased in tumor tissue, suggesting a shift of oxidative metabolisms, a pro-oxidation state, and potential gene instability in malignant ovary cells [31]. *Senthil et al.* obtained similar results in a group of 30 women with ovarian cancer. This study's authors demonstrated a decreased activity/concentration of SOD, CAT, and antioxidants of vitamin C and E. They suggested that this may be due to their increased use for lipid peroxide capture and sequestration by cancer cells. Increased lipid peroxidation levels may result from excessive oxidative stress caused by continual ovulation or epithelial inflammation [29].

Gorozhanskaia et al. obtained different results. They showed increased CAT activity and SOD activity in platelets in patients in stages

3–4 of the disease. These results may mean that the impact made by deranged free radicals' regulations on the platelet chain in the hemostasis system causes changes in the blood rheological properties entailing, a higher aggregation of platelets triggering the onset of platelet-embolic complications in the discussed patient category. The impaired regulation mechanism of antioxidant protection in platelets is a significant manifestation of the oxidant stress evolving due to a growing tumor. The mechanism is essential in evaluating the structural and functional platelets' condition [32].

Caglayan et al. emphasized the importance of hormones in the development of ovarian cancer, and together with a disturbed redox balance, may play a vital role in the pathogenesis of epithelial ovarian cancer. As ovarian epithelial tumors are typically sensitive to redox imbalance, the development of therapies targeting mainly manganese superoxide dismutase (Mn-SOD) and CAT may provide important insights for the prevention and/or treatment of EOC. Additionally, these findings may contribute to continued improvements in cancer treatment research [33].

6. Colorectal cancer

Colorectal cancer has a globally high death rate. Colorectal cancer is the second most frequently diagnosed cancer in women and the third in men. Colorectal cancer is characterized by uncontrolled cell growth in the colon and rectum [34,35]. It is believed that factors such as improper diet, obesity, smoking, and excessive alcohol consumption can increase the risk of colorectal cancer. However, the etiology and pathogenesis are still unclear [34,35].

Recent studies have shown the critical role of ROS in colorectal cancer carcinogenesis. Mitochondria are the primary ROS source, and mutations of mitochondrial DNA are often observed in various types of cancer, including colon cancer [35]. Mitochondria play an essential role in the production of cellular ATP through oxidative phosphorylation and also regulate the aging process, ROS production, and apoptosis. Thus, mitochondria act as a switch between cell death and abnormal cell growth [33].

Human mitochondrial DNA (MtDNA) is a circular, double-stranded DNA molecule. MtDNA has a higher mutation rate than nuclear DNA and is more susceptible to oxidative damage. This is due to the lack of protective histone proteins, limited DNA repair mechanisms, and a high generation of reactive oxygen species [35].

Reactive oxygen species such as peroxide (O2–) and hydrogen peroxide are produced continuously in the mitochondria due to imperfect flow through the electron transport chain. A moderate increase in ROS may stimulate cell growth and proliferation, while excessive accumulation leads to cellular damage of the DNA structure, protein, or lipid membrane. Under physiological conditions, ROS production is balanced by different antioxidant enzymes including SOD. Mitochondrial SOD contains manganese (MnSOD), necessary for the conversion of peroxide to hydrogen peroxide, which is then eliminated by other antioxidant enzymes. Since mitochondrial chain electron transport is the central place where O2– is produced, MnSOD plays a significant role in maintaining the cellular balance of reactive oxygen species [35].

Elevated oxidative stress levels have been reported in many different diseases, including colorectal cancer. Increased ROS production may be related to the activity of cellular metabolism caused by oncogenic signals and/or the abnormal mitochondria functioning in neoplastic cells. It appears that oxidative stress makes cancer cells more dependent on mitochondrial MnSOD to protect themselves from O2– damage [35].

To clarify if mitochondrial changes in MnSOD are related to intestinal cancer carcinogenesis. Govatati et al. examined 35 tissue specimens from colorectal cancer patients and compared them to healthy tissues. Patients diagnosed with other pre-existing malignant neoplasms, familial adenomatous polyposis, ulcerative colitis, and Crohn's disease were excluded from the study. All patients had adenocarcinoma and were classified according to the clinical staging system. The patients consisted of 4 – T1 cases, 9 – T2 cases, 17 – T3 cases, and 5 – T4 cases [36].

Western Blot analysis revealed increased MnSOD expression in neoplastic tissues compared to normal tissues (Fig. 3). Despite that abnormal MnSOD expression has been identified earlier in several diseases, fewer studies have documented abnormal MnSOD activity in colorectal cancer. Moreover, MnSOD expression appeared to be related to the degree of microsatellite instability of mitochondrial DNA and the degree of tumor advancement. The level of MnSOD expression was significantly higher in the advanced stages of tumors with a high degree of mitochondrial DNA microsatellite instability [35].

A study conducted by Janssen et al. showed increased MnSOD expression in the colon's neoplastic tissue compared to normal tissue [36]. Toh et al. also conducted a study in which they found increased expression of MnSOD in colorectal cancer compared to the corresponding normal tissues. It was also shown that tissues with MnSOD overexpression were characterized by a higher frequency of venous invasion and more frequent metastases to the lymph nodes [37]. More studies are suggesting that neoplasms in advanced stages produce large amounts of reactive oxygen species and are frequently under the influence of oxidative stress [37].

MnSOD expression, and its ability to react to oxidative stress, rapidly ensure adequate cellular ROS levels. The loss of such an antioxidant mechanism would lead to O2– accumulation, which is responsible for stimulating cell proliferation and tumor growth. It has been found that a response to intrinsic oxidative stress most likely causes increased expression in tumors, therefore increased MnSOD expression may prevent further elevation of O2– levels and thus may reduce its stimulating effect on cell proliferation. Because of this, MnSOD may be considered a protective enzyme capable of counteracting reactive oxygen species' harmful effects, including stimulating cell growth and causing DNA structural damage [35].

Zinczuk et al. conducted the world's first clinical trial to assess antioxidant activity in patients with colorectal cancer (CRC). They demonstrated that SOD activity was significantly higher whereas CAT, GPx, and GR activity was considerably lower in CRC patients compared to the control group. They also stated that redox biomarkers could be potential diagnostic indicators of CRC advancement. However, more clinical trials are needed to investigate the relationship between antioxidant enzymes activity and the stage, type, and prognosis of patients with CRC [38].

In another study, Zińczuk et al. conducted a similar study on 29

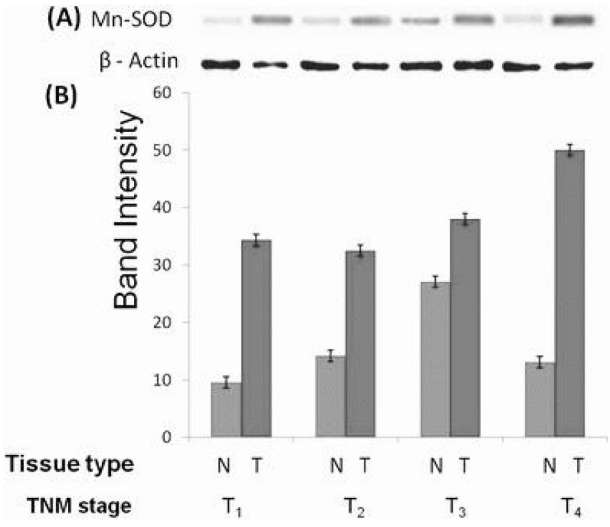

Fig. 3. Western blot analysis of Mn-SOD expression: **A)** representative Western immunoblot for Mn-SOD; **B)** densitometric analysis of band intensity. Each column represents the mean (±SD) of band intensity. T – tumor tissue, N – normal tissue [35].

people with colorectal cancer. They showed an increase in the activity of XOR, CAT, SOD, NADPH oxidase, and the level of TAC (total antioxidant) in tumor tissue compared to healthy colon mucosa. They also showed a relationship between CAT activity and the intensity of the inflammatory tumor infiltration. These results confirm that CRC is associated with enzymatic/non-enzymatic redox imbalance and increased oxidative damage to proteins, lipids, and DNA. The determination of these biomarkers could be useful for the evaluation of tumor progression [39]. Many researchers over the years have obtained similar results [40,41,42].

Skrzycki et al. demonstrated a relationship between the degree of CRC advancement and differentiation of neoplastic cells and the activity of SOD and the level of AP-1 and NF-kappaB proteins. They also showed that cancer cells adapt to increased oxidative stress and suggest an impairment of processes regulated by AP-1 and NF-kappaB, which are critical for tumor progression (proliferation, differentiation, and apoptosis) [43].

Gulubova et al., in turn, showed that increased expression of GST might indicate poor prognosis in patients with colorectal cancer. They also suggest that the presence of endocrine cells in tumors with an activated antioxidant defense and possibly more metabolically active may determine a more aggressive type of cancer, leading to a worse prognosis for patients [44].

Marjaneh et al. have shown that the use of phytosomal curcumin and 5-fluorouracil in a murine colon cancer model reduces the number of tumors in both the middle and distal colon and causes a decrease in CAT activity. It may mean that catalase may be a prognostic marker in treating colorectal cancer [45].

The studies presented above show that antioxidant enzymes are essential in diagnosing and monitoring the patient's condition and predictive in the treatment of colorectal cancer (such as CAT).

Maffei et al. conducted a screening study for CRC prevention on 82 people. This study showed increased CAT activity and decreased SOD in patients with colorectal cancer compared to people with intestinal polyps and control groups. GST activities between the groups did not differ significantly. These results can help define plasma biomarkers associated with oxidative stress damage predictive of CRC cancer risk [46].

On the other hand, *Kocot et al.* indicate the importance of SOD and TAS (antioxidant status) in CRC treatment. They showed an increase in SOD and TAS activity/levels in colon tumors compared to normal colon tissue in stages I-III and decreased stage IV, respectively [47].

Another study also indicates the potential importance of SOD in the treatment of patients with colorectal cancer. *Ribeiro et al.* demonstrated that zinc supplementation during chemotherapy cycles increased SOD activity and maintained vitamin E concentration. However, they did not observe zinc supplementation on markers of oxidative stress in this study. An increase in SOD activity indicates the production of stable free radicals, which may positively affect cancer treatment [48].

7. Conclusions

Research carried out in the last 20 years indicates the increasing use of antioxidant enzymes as biomarkers for diagnostics, monitoring the condition of patients, chemotherapy as prognostic factors, and informing about the stage of cancer and its type. Of particular importance in diagnosis and prognostic factors are enzymes such as CAT and SOD in bladder cancer; SOD, CAT, and GST in lung cancer; XOR, CAT, and SOD ovarian cancer or SOD, CAT, GPx, GR in colorectal cancer. Despite enormous advances in research into antioxidant enzymes as biomarkers, more clinical trials are still needed. The research results presented in this paper show the enormous potential of antioxidant enzymes in oncology and bring them closer to the introduction of tests of their activity in routine diagnostics.

References

[1] Zalewska-Ziob M., Adamek B.,Kasperczyk J., Romuk E., Hudziec E., Chwalińska E., Dobija-Kubica K., Rogoziński P, Bruliński K., Activity of Antioxidant Enzymes in the Tumor and Adjacent Noncancerous Tissues of Non-Small-Cell Lung Cancer, Oxid Med Cell Longev. 31; 2019:2901840.

[2] E. Gałecka, R. Jacewicz, M. Mrowiska, A. Florkowski, P. Gałecki, Antioxidant enzymes – structure, properties and functions, Pol. Merk. Lek. 147 (2008) 266–268.

[3] T. Wielkoszyński, M. Zawadzki, A. Lebek-Ordon, J. Olek, I. Korzonek-Szlacheta, Enzymatic antioxidant systems – properties, occurrence and biological role, Diagnostyka lab. 43 (2007) 283–294.

[4] E. Cecerska-Heryć, Activity of antioxidant enzymes in platelets in patients with chronic kidney disease, MA thesis, Pomeranian Medical University, Szczecin, 2016.

[5] E. Cecerska-Heryć, A. Jesionowska, K. Szupiluk, K. Siewierska, D. Mączka, D. Pawlak, M. Urbańska, B. Dołęgowska, Xanthine oxidoreductase reference values in platelet-poor plasma and platelets in healthy volunteers, Oxid. Med. Cell Longev. 2015 (2015), 341926.

[6] M.G. Battelli, L. Polito, M. Bortolotti, A. Bolognesi, Xanthine oxidoreductase in cancer: more than a differentiation marker, Cancer Med. 5 (3) (2016) 546–557.

[7] WHO: World Cancer Report 2014. World Health Organization, Feb 2014.

[8] V.L. Kinnula, J.D. Crapo, Superoxide dismutases in the lung and human lung diseases, Am. J. Respir. Crit. Care Med. 167 (12) (2003) 1600–1619.

[9] H.J. Chung-man, S. Zheng, S.A. Comhair, C. Farver, S.C. Erzurum, Differential expression of manganese superoxide dismutase and catalase in lung cancer, Cancer Res. 61 (23) (2001) 8578–8585.

[10] H. Kaynar, M. Meral, H. Turhan, M. Keles, G. Celik, F. Akcay, Glutathione peroxidase, glutathione-S-transferase, catalase, xanthine oxidase, Cu-Zn superoxide dismutase activities, total glutathione, nitric oxide, and malondialdehyde levels in erythrocytes of patients with small cell and non-small cell lung cancer, Cancer Lett. 227 (2) (2005) 133–139.

[11] Carpagnano GE, Lacedonia D, Palladino GP, Koutelou A, Martinelli D, et al.: Could exhaled ferritin and SOD be used as markers for lung cancer and prognosis prediction purposes? Eur J Clin Invest. 2012 May; 42(5):478-86.

[12] A. Luengo, K.L. Abbott, S.M. Davidson, A.M. Hosios, B. Faubert, S.H. Chan, E. Freinkman, L.G. Zacharias, T.P. Mathews, C.B. Clish, R.J. DeBerardinis, C. A. Lewis, M.G. Vander Heiden, Reactive metabolite production is a targetable liability of glycolytic metabolism in lung cancer, Nat. Commun. 10 (1) (2019).

[13] S.-C. Tang, G.-T. Sheu, R.-H. Wong, C.-Y. Huang, M.-W. Weng, L.-W. Lee, C.-P. Hsu, J.-L. Ko, Expression of glutathione S-transferase M2 in stage I/II non-small cell lung cancer and alleviation of DNA damage exposure to benzo[a]pyrene, Toxicol. Lett. 192 (3) (2010) 316–323.

[14] D. Diksha, P. Gupta, P.S. Malik, A. Mohan, A pilot study to assess oxidative and inflammatory markers as early indicator for response to chemotherapy in non-small cell lung cancer, J. Clin. Pharm. Ther. 45 (1) (2020) 179–184.

[15] A.W. Kim, M. Batus, R. Myint, M.J. Fidler, S. Basu, P. Bonomi, L.P. Faber, S. C. Wightman, W.H. Warren, M. McIntire, L.D. Arvanitis, P. Gattuso, X. Xu, M. J. Liptay, Prognostic value of xanthine oxidoreductase expression in patients with non-small cell lung cancer, Lung Cancer. 71 (2) (2011) 186–190.

[16] H. Konno, Y. Minamiya, H. Saito, K. Imai, Y. Kawaharada, S. Motoyama, J.-I. Ogawa, Acquired xanthine dehydrogenase expression shortens survival in patients with resected adenocarcinoma of lung, Tumour Biol. 33 (5) (2012) 1727–1732.

[17] M.O. Islam, T. Bacchetti, G. Ferretti, Alterations of antioxidant enzymes and biomarkers of nitro-oxidative stress in tissues of bladder cancer, Oxid. Med. Cell. Longev. 2019 (2019) 1–10.

[18] I. Durak, H. Perk, M. Kavutçu, O. Canbolat, O. Akyol, Y. Bedük, Adenosine deaminase, 5'nucleotidase, xanthine oxidase, superoxide dismutase, and catalase activities in cancerous and noncancerous human bladder tissues, Free Radic. Biol. Med. 16 (6) (1994) 825–831.

[19] S.H. Jeon, J.H. Park, S.G. Chang, Expression of antioxidant enzymes (catalase, superoxide dismutase, and glutathione peroxidase) in human bladder cancer, Korean J. Urol. 48 (9) (2007) 921–926.

[20] İ. Gecit, R. Eryılmaz, S. Kavak, İ. Meral, H. Demir, N. Pirinççi, M. Güneş, K. Taken, The prolidase activity, oxidative stress, and nitric oxide levels of bladder tissues with or without tumor in patients with bladder cancer, J. Membr. Biol. 250 (5) (2017) 455–459.

[21] K.M. Connor, N. Hempel, K.K. Nelson, G. Dabiri, A. Gamarra, J. Belarmino, L. Van De Water, B.M. Mian, J.A. Melendez, Manganese superoxide dismutase enhances the invasive and migratory activity of tumor cells, Cancer Res. 67 (21) (2007) 10260–10267, https://doi.org/10.1158/0008-5472.CAN-07-1204. PMID: 17974967.

[22] S. Arikan, T. Akcay, D. Konukoglu, C. Obek, A.R. Kural, The relationship between antioxidant enzymes and bladder cancer, Neoplasma. 52 (4) (2005) 314–317.

[23] E. Wieczorek, Z. Jablonowski, B. Tomasik, J. Gromadzinska, E. Jablonska, T. Konecki, W. Fendler, M. Sosnowski, W. Wasowicz, E. Reszka, Different gene expression and activity pattern of antioxidant enzymes in bladder cancer, Anticancer Res. 37 (2) (2017) 841–848.

[24] N. Bayraktar, S. Kilic, M.R. Bayraktar, N. Aksoy, Lipid peroxidation and antioxidant enzyme activities in cancerous bladder tissue and their relation with bacterial infection: a controlled clinical study, J. Clin. Lab. Anal. 24 (1) (2010) 25–30.

[25] N. Linder, R. Bützow, H. Lassus, M. Lundin, J. Lundin, Decreased xanthine oxidoreductase (XOR) is associated with a worse prognosis in patients with serous ovarian carcinoma, Gynecol. Oncol. 124 (2) (2012) 311–318.

[26] J. Didžiapetrienė, J. Bublevič, G. Smailytė, B. Kazbarienė, R. Stukas, Significance of blood serum catalase activity and malondialdehyde level for survival prognosis of ovarian cancer patients, Medicina (Kaunas). 50 (4) (2014) 204–208.
[27] A. Jesionowska, E. Cecerska-Heryc, N. Matoszka, B. Dolegowska, Lysophosphatidic acid signaling in ovarian cancer, J. Recept. Signal Transduct. Res. 35 (6) (2015) 578–584.
[28] Manimaran A., Rajneesh C.P., Activities of Antioxidant Enzyme and Lipid Peroxidation in Ovarian Cancer Patients, Academic Journal of Cancer Research 2. 2009; (2):68-72.
[29] K. Senthil, S. Aranganathan, N. Nalini, Evidence of oxidative stress in the circulation of ovarian cancer patients, Clin. Chim. Acta 339 (1-2) (2004) 27–32.
[30] A. Ramadan, R. Hemida, A. Nowara, L.A. Eissa, A.M. El-Gayar, Role of oxidative stress in epithelial ovarian cancer in Egyptian patients, J. Exp. Ther. Oncol. 12 (1) (2017) 9–15.
[31] M. Sanchez, J.V. Torres, C. Tormos, A. Iradi, P. Muñiz, O. Espinosa, A. Salvador, J. Rodriguez-Delgado, M. Fandos, G.T. Sáez, Impairment of antioxidant enzymes, lipid peroxidation and 8-oxo-2'-deoxyguanosine in advanced epithelial ovarian carcinoma of a Spanish community, Cancer Lett. 233 (1) (2006) 28–35.
[32] E.G. Gorozhanskaia, T.V. Davydova, G.N. Zubrikhina, N.G. Kormosh, K. P. Laktionov, Antioksidantnaia sistema trombotsitov u bol'nykh rakom iaichnikov [Antioxidant system of platelets in patients with ovary cancer], Klin. Lab. Diagn. 10 (2003) 41–44.
[33] A. Caglayan, D.C. Katlan, Z. Selçuk Tuncer, K. Yüce, H.B. Sayal, M. Coşkun Salman, B. Kocer-Gumusel, Impaired antioxidant enzyme functions with increased lipid peroxidation in epithelial ovarian cancer, IUBMB Life 69 (10) (2017) 802–813.
[34] P. Su, V.P. Veeraraghavan, S. Krishna Mohan, W. Lu, A ginger derivative, zingerone-a phenolic compound-induces ROS-mediated apoptosis in colon cancer cells (HCT-116), J. Biochem. Mol. Toxicol. 33 (12) (2019).
[35] S. Govatati, S. Malempati, B. Saradamma, D. Divyamaanasa, B.P. Naidu, P. V. Bramhachari, N. Narayana, S. Shivaji, M. Bhanoori, R.R. Tamanam, P.S. Rao, V. Nallanchakravarthula, Manganese-superoxide dismutase (Mn-SOD) overexpression is a common event in colorectal cancers with mitochondrial microsatellite instability, Tumour Biol. 37 (8) (2016) 10357–10364.
[36] A.M.L. Janssen, C.B. Bosman, L. Kruidenier, G. Griffioen, C.B.H.W. Lamers, J.H.J. M. van Krieken, C.J.H. van de Velde, H.W. Verspaget, Superoxide dismutases in the human colorectal cancer sequence, J. Cancer Res. Clin. Oncol. 125 (6) (1999) 327–335.
[37] Y. Toh, S. Kuninaka, T. Oshiro, Y. Ikeda, H. Nakashima, H. Baba, S. Kohnoe, T. Okamura, M. Mori, K. Sugimachi, Overexpression of manganese superoxide dismutase mRNA may correlate with aggressiveness in gastric and colorectal adenocarcinomas, Int. J. Oncol. 17 (1) (2000) 107–112.
[38] Zińczuk J., Maciejczyk M., Zaręba K., Romaniuk W., Markowski A., et al.: Antioxidant Barrier, Redox Status, and Oxidative Damage to Biomolecules in Patients with Colorectal Cancer. Can Malondialdehyde and Catalase Be Markers of Colorectal Cancer Advancement? Biomolecules. 2019 Oct 22; 9(10):637.
[39] Zińczuk J, Maciejczyk M, Zaręba K, Pryczynicz A, Dymicka-Piekarska V, et al.: Pro-Oxidant Enzymes, Redox Balance and Oxidative Damage to Proteins, Lipids and DNA in Colorectal Cancer Tissue. Is Oxidative Stress Dependent on Tumour Budding and Inflammatory Infiltration? Cancers (Basel). 2020 Jun 20; 12(6):1636.
[40] K. Malinowska, M. Mik, Ł. Dziki, A. Dziki, I. Majsterek, Evaluation of antioxidant defense in patients with colorectal carcinoma, Pol. Przegl Chir. 87 (7) (2015) 357–361, https://doi.org/10.1515/pjs-2015-0069. PMID: 26351790.
[41] H. Czeczot, M. Skrzycki, M. Podsiad, E. Gawryszewska, P. Nyckowski, Z. Porembska, Antioxidant status of patients with primary colorectal cancer and liver metastases of colorectal cancer, Pol. Merkur. Lekarski. 18 (103) (2005) 58–61.
[42] I.L.G. Farias, J.G. Farias, L. Rossato, M.C.S. Araújo, J. Chiesa, V. Morsh, M.R. C. Schetinger, Correlation between TBARS levels and glycolytic enzymes: the importance to the initial evaluation of clinical outcome of colorectal cancer patients, Biomed. Pharmacother. 65 (6) (2011) 395–400.
[43] M. Skrzycki, M. Majewska, M. Podsiad, H. Czeczot, Expression and activity of superoxide dismutase isoenzymes in colorectal cancer, Acta Biochim. Pol. 56 (4) (2009) 663–670.
[44] M. Gulubova, T. Vlaykova, Expression of the xenobiotic- and reactive oxygen species-detoxifying enzymes, GST-pi, Cu/Zn-SOD, and Mn-SOD in the endocrine cells of colorectal cancer, Int. J. Colorectal Dis. 25 (12) (2010) 1397–1405.
[45] R.M. Marjaneh, F. Rahmani, S.M. Hassanian, N. Rezaei, M. Hashemzehi, A. Bahrami, F. Ariakia, H. Fiuji, A. Sahebkar, A. Avan, M. Khazaei, Phytosomal curcumin inhibits tumor growth in colitis-associated colorectal cancer, J. Cell Physiol. 233 (10) (2018) 6785–6798.
[46] F. Maffei, C. Angeloni, M. Malaguti, J.M.Z. Moraga, F. Pasqui, C. Poli, A. Colecchia, D. Festi, P. Hrelia, S. Hrelia, Plasma antioxidant enzymes and clastogenic factors as possible biomarkers of colorectal cancer risk, Mutat Res. 714 (1-2) (2011) 88–92.
[47] Kocot J, Kiełczykowska M, Dąbrowski W, Piłat J, Rudzki S, Musik I. Total antioxidant status value and superoxide dismutase activity in human colorectal cancer tissue depending on the stage of the disease: a pilot study. Adv Clin Exp Med. 2013 May-Jun; 22(3):431-7.
[48] S.M.d.F. Ribeiro, C.B.M. Braga, F.M. Peria, F.A. Domenici, E.Z. Martinez, O. Feres, J.J.R.d. Rocha, S.F.d.C.d. Cunha, Effect of zinc supplementation on antioxidant defenses and oxidative stress markers in patients undergoing chemotherapy for colorectal cancer: a placebo-controlled, prospective randomized trial, Biol. Trace Elem. Res. 169 (1) (2016) 8–16.