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A potential chemopreventive activity of tamoxifen and amygdalin on oxidative stress in mammary carcinoma-induced in female mice.

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ABSTRACT

This study was undertaken to investigate the potential effect of tamoxifen and amygdalin in mammary carcinoma induced in mice. Fifty female albino mice, 4-6 weeks old age, were divided into five equal groups: group I (control normal) administrated no drugs; group II (carcinogenic group) administrated 7,12-dimethylbenz[a]anthracene (DMBA) dissolved in sesame oil (50 mg/kg b.wt) once a weak orally for 4 weeks; group III (tamoxifen treated group) given tamoxifen (50 mg/kg b.wt/day) orally for 4 weeks after induction of mammary cancer; group IV (amygdalin treated group) treated with amygdalin (0.6 mg/kg b.wt/day) for 4 weeks after induction of mammary carcinoma; group V (tamoxifen + amygdalin treated group) administrated tamoxifen as in group (III) with amygdalin as in group (IV). The obtained results exhibited that DMBA-induced mammary carcinomas caused a significant increase in serum progesterone and mammary tissue L-malondialdehyde (L-MDA) concentrations, with significant decrease in total antioxidant capacity (TAC) as compared to the control group. However, the administration of tamoxifen and amygdalin alleviates DMBA-induced mammary carcinomas through decreasing serum progesterone and L-MDA concentrations, along with increasing TAC concentration in mammary tissue. Additionally, hematological parameters of tamoxifen and amygdalin-treated mice displayed a significant increase compared to mammary cancer treated mice. Thus, it can be concluded that tamoxifen with amygdalin may be successful in the treatment of mammary carcinoma as well as improvement of oxidative stress of mammary carcinoma tissue.

1. INTRODUCTION

Cancer is a major risk to health and life. Breast cancer is the most commonly diagnosed cancer which leads to death in females in the world (Juanjuan et al., 2017). Accordance to the statistics, 5-10% of breast cancers are believed to be hereditary cause, and over 90% of breast cancers are caused by other factors, such as environmental and lifestyle factors (e.g. diet), that make a dangerous effect on the relevance of breast cancer (Nguyen et al., 2017).

Although the presence of various tumor treatments comprising surgery, radiotherapy, chemotherapy, and immunotherapy, the mortality rate with malignant tumors is still high (Yang, 2012). More efforts have been struggled to realize natural and synthetic antitumor with antioxidant efficacy. Therefore, some trials have been carried out and the obtained results showed the dual synergistic effect between synthetic antitumor and natural agents (Badawy et al., 2021). Diseases have been treated with natural medicines for millennia. Antioxidant and anti-inflammatory properties of amygdalin have been reported (Orlikova et al., 2014). The anticancer action of amygdalin was first described in the Journal of the National Cancer Institute (JNCI) by Lea et al., (1979).

Amygdalin is a cyanogenic chemical found in the family of aromatic cyanogenic glycosides; it is also known as bitter apricot, laetrile, and almond. Amygdalin is found in a variety of plant parts, although it is most concentrated in the seeds of rosaceous plants like apricots, peaches, cherries, plums, etc. (Santos et al., 2019).

Amygdalin is mainly as an alternative therapy for traditional cancer treatment, or combined with other nonconventional treatments, such as metabolic therapy, urine therapy, dietotherapy, intake of fruit seeds, intravenous injection of β-glucosidases and so on. β-glucosidases enzyme was found from the intestinal bacteria, it also can be found in edible plants, with function of decomposing amygdalin into benzaldehyde, glucose and hydrocyanic acid. Amygdalin exists in the related products of amygdalin and Laetrile, is the active component of drugs (Zhou et al., 2012).

In addition, tamoxifen is a medication used to treat breast cancer in both males and females by preventing the cancer from spreading (Gucalp et al., 2019). The breast cancer treatment Tamoxifen has mixed estrogenic and antiestrogenic activity, with its profile of differing by tissue. For example, tamoxifen has predominantly antiestrogenic effects in the breasts but predominantly estrogenic effects in the uterus (Wang et al., 2004). Thus, it is suggested for premenopausal and postmenopausal females with estrogen receptor-positive breast cancer at any stage (Burstein et al., 2014).

Accordingly, the potential synergistic effect of antitumor drugs tamoxifen with natural agent amygdalin were evaluated in mammary cancers induced in mice.

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2. MATERIAL AND METHODS

2.1. Chemicals:

2.1.1. *7, 12-Dimethylbenz[a]anthracene (DMBA):* DMBA purchased from Sigma-Aldrich Chemical Co., ID. NO. 24891046, and provided by Egyptian International Center for Import Cairo, Egypt); in the form of powder with chemical formula C20H16, molecular weight 256.341 g/mol. DMBA were dissolved in 100% sesame oil and administered orally for induction of mammary tumor at a dose of (50 mg/kg b.wt /once a week) for 4 weeks (Minari and Okeke 2014).

2.1.1. *Amygdaline:* D-Amygdalin were purchased from Sigma-Aldrich Chemical Co. (St. Louis, MO, USA); ID.NO. 24891046; in the form of crystalline powder with chemical formula $C_{20}H_{27}NO_{11}$, molecular weight 457.44 Dalton. Amygdaline was dissolved in 100% corn oil and administered orally at a dose of (o.6 mg/kg b. wt /day) (Bromley et al., 2005).

2.1.2. *Tamoxifen* (Nolvadex-D) ®: Chemical anticancer drug, manufactured by (AstraZenica group. AstraZenica©2000, UK limited) in the form of tablet and each tablet contain (20 mg) and dissolved in distilled water with chemical formula $C_{26}H_{29}NO$ and molecular weight 371.515 g/mol. Tamoxifen was administered orally at a dose (50 mg/kg b.wt/day) for 4 weeks (Fendl and Zimniski, 1992).

2.2. Experimental animals:

Fifty female albino mice, 4 to 6 weeks of age and weighing 18 to 35 g were used in this study (Karimi et al., 2019). Mice were purchased from Animal Research Center, Faculty of Veterinary Medicine, Benha University. Animals were isolated in metal cages with controlled temperatures and diets for the duration of the study. The animals were given a steady diet of food and access to water at all times. Mice were allowed to acclimatize at animal facility for at least one week before the start of experiment. The Ethical Committee of the School of Veterinary Medicine at Benha University reviewed and approved all experimental procedures (BUFVTM 18-01-23).

2.3. Experimental design:

Female mice were randomly divided into five main equal groups, 10 mice each, placed in individual cages, and classified as follows:

Group I (Normal control): female mice received no drugs, served as control non- treated for all experimental groups.

Group II: (carcinogenic induced group): female mice administrated oral DMBA at a dose of (50 mg/kg b.wt orally once a week) in sesame oil at 5 weeks of age for 4 weeks (Minari and Okeke 2014).

Group III: (Tamoxifen treated group) female mice received tamoxifen orally at a dose (50 mg/kg b.wt/day) dissolved in distilled water for 4 weeks (Fendl and Zimniski, 1992).

Group IV: (Amygdalin treated group) female mice administrated with Amygdalin (0.6 mg/kg b.wt/day) orally in 100% corn oil for 4 weeks (Bromley et al., 2005).

Group V: (Tamoxifen + Amygdalin treated group) female mice treated orally with tamoxifen (50 mg/kg b.wt/day) dissolved in distilled water (Fendl and Zimniski, 1992) and amygdalin (0.6 mg/kg b.wt/day) in 100% corn oil for 4 weeks (Bromley et al., 2005).

2.4. Sampling:

2.4.1 Blood samples:

Blood samples were taken from mice at the end of the experiment and divided into two parts: one put in EDTA tube for hematological parameters analysis, and the other put in plain tube to obtain the serum after centrifugation at 3000 rpm for 15 min. The clear serum was collected using an automated pipette, placed in a dry sterile samples tube, and stored in the freezer at -20 °C till do the biochemical analysis for progesterone hormone concentration.

2.4.2 Tissue Samples (mammary tissues):

Mice were anesthetized prior sacrificed according to Marquardt et al., (2018) when their experimentation time was up. To analyze oxidative stress indicators L-MDA and TAC, the mammary tissues were rapidly removed and frozen at -80 °C.

2.5. Assay methods:

2.5.1. Hematological Analysis:

An automated hematological analyzer was used for the blood count (Abbott Cell-Dyn 3500 Hematology Analyzer). Hemoglobin (Hb), red blood cell count (RBCs), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), platelets, white blood cell count (WBCs), and differential white blood cell count (neutrophils, lymphocytes, monocytes, eosinophils, and basophils) were all measured (Charles et al., 2007).

2.5.2. Serum biochemical analysis:

The concentration of progesterone was determined using a Chinese instrument, the AutoLumo A1000, and the manufacturer-recommended reagent kits (Autobio Diagnostics Co., LTD), CAT NO. CL1106-2, as described by Daly et al. (2017).

2.5.2. Tissue oxidative stress:

Mammary tissues were cut and washed with a PBS (phosphate buffered saline) solution, pH 7.4 containing 0.16 mg/ml heparin to remove any red blood cells and clots. Homogenization of one-gram mammary tissue took place in 5 ml cold buffer (i.e., 50mM potassium phosphate, PH 7.5 1mM EDTA), using sonicator homogenizer. Aliquots of tissue homogenates was centrifuged by cooling centrifuge 4000rpm for 20min then the supernatant was removed and stored at -20˚C till do the oxidative stress. TAC and L-MDA concentrations were determined by Spectro nanodrop using commercial kits (Biodiagnostic, Cairo, Egypt, CAT. NO. TA2513; MD2529) according to (Korcevic et al., 2011), (Satoh, 1978) using the supernatants from the homogenates centrifuged at 8000 rpm for 20 minutes at 4 °C.

2.6. Statistical analysis:

Two-way analysis of variance (ANOVA) and Duncan's multiple tests were used for statistical analysis of the data collected. All calculations were done with the help of the social science statistics program (SPSS, 13.0 software, 2005). To indicate statistical significance, P values below 0.05 were used.

3.RESULTS

The obtained hematological parameters results showed a significant decrease in Hb concentration, RBCs count, HCT, as well as platelets count in DMBA - induced mammary cancer mice, with a significant increase in WBCs and its differential counts (neutrophils; lymphocytes; monocytes; eosinophils; basophils) when compared with control normal

group; but MCV, MCH and MCHC not significantly altered. On the other hand, treatment of mammary cancer mice with amygdalin insignificantly improved Hb level and not significantly altered MCV, MCH and MCHC. WBCs didn't improve by amygdalin administrations, but their differential counts reached control values. Moreover, treating DMBA-bearing mice with tamoxifen revealed decline in Hb level, Hct, as well as platelets count with decrease of WBCs, but their differential counts were improved. Interestingly, amygdalin with tamoxifen altogether administration resulted in a significant improvement in all previous parameters when compared with DMBA-non treated mice throughout the experimental periods (after 2 weeks and 4 weeks); all these data are listed in tables (1), (2).

According to serum biochemical analysis, the obtained results revealed that DMBA-induced mammary tumors exhibited significant increase in serum progesterone hormone concentration as compared to control normal mice. Conversely, amygdalin and tamoxifen administrations resulted in significant improvement in serum progesterone level after 2 weeks and 4 weeks in comparison with mammary cancer non treated group; as shown in table (3).

Regarding oxidative stress biomarkers, mammary tissue L-malondialdehyde (L-MDA) concentration was significantly increased in DMBA-induced mammary cancer mice followed by obvious decrease after amygdalin and tamoxifen administration (Fig. 14 and table 3). Also, total antioxidant capacity (TAC) in mammary tissue was distinctly increased after amygdalin and tamoxifen administration during the experimental period, especially after 4 weeks, when compared with mammary cancer non treated mice (table 3).

Table 1 Effect of tamoxifen and amygdalin administration on hematological parameters in DMBA-induced mammary carcinoma in female mice.

		Hb (g/dL)	RBCS ($\times10^6$/µL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (%)	Platlets ($\times10^3$/µL)
Control	2nd WK	9.87±0.20 ^{Aa}	3.37±0.09 ^{Aa}	28.47±0.58 ^{Aa}	84.67±0.52 ^{Aa}	29.27±0.17 ^{Aa}	34.60±0.00 ^{Aa}	513.33±14.53 ^{Ab}
	4th WK	9.89±0.21 ^{Aa}	3.38±0.09 ^{Aa}	28.49±0.57 ^{Aa}	84.69±0.53 ^{Aa}	29.29±0.19 ^{Aa}	34.60±0.00 ^{Aa}	513.35±14.54 ^{Aa}
DMBA	2nd WK	8.59±0.29 ^{Ab}	2.87±0.12 ^{Ac}	24.77±0.84 ^{Ab}	85.73±0.48 ^{Aa}	29.97±0.41 ^{Aa}	34.60±0.00 ^{Aa}	190.33±3.18 ^{Ad}
	4th WK	7.30±0.23 ^{Bd}	2.50±0.12 ^{Ac}	21.43±1.00 ^{Ac}	85.80±0.75 ^{Aa}	29.70±0.25 ^{Aa}	34.60±0.00 ^{Aa}	141.67±10.14 ^{Bc}
tamoxifen	2nd WK	8.60±0.12 ^{Ab}	2.91±0.07 ^{Abc}	24.80±0.35 ^{Ab}	84.43±0.78 ^{Aa}	29.50±0.60 ^{Aa}	34.60±0.00 ^{Aa}	405.00±31.75 ^{Ac}
	4th WK	7.89±0.11 ^{Bc}	2.73±0.09 ^{Ac}	23.07±0.59 ^{Ac}	84.57±0.52 ^{Aa}	29.23±0.20 ^{Aa}	34.60±0.00 ^{Aa}	246.67±13.02 ^{Bb}
Amygdalin	2nd WK	9.87±0.20 ^{Aa}	3.37±0.09 ^{Aa}	28.47±0.58 ^{Aa}	84.67±0.52 ^{Aa}	29.27±0.17 ^{Aa}	34.60±0.00 ^{Aa}	681.67±33.21 ^{Aa}
	4th WK	8.93±0.09 ^{Bb}	3.10±0.05 ^{Ab}	26.17±0.62 ^{Ab}	84.33±0.68 ^{Aa}	29.13±0.23 ^{Aa}	34.60±0.00 ^{Aa}	502.33±30.31 ^{Ba}
tamoxifen + amygdalin	2nd WK	9.30±0.12 ^{Aa}	3.17±0.03 ^{Aab}	26.80±0.35 ^{Aa}	84.80±0.52 ^{Aa}	29.32±0.16 ^{Aa}	34.60±0.00 ^{Aa}	552.33±1.45 ^{Ab}
	4th WK	8.43±0.21 ^{Bbc}	3.01±0.06 ^{Ab}	25.27±0.58 ^{Ab}	84.03±0.38 ^{Aa}	29.03±0.13 ^{Aa}	34.60±0.00 ^{Aa}	471.67±30.32 ^{Aa}

(DMBA: 7,12-dimethylbenz[a]anthracene).
Data are presented as (Mean ± S.E). SE: Standard error.
a, b, c: Mean values with different superscript letters in the same column refers to different groups at the same time are significantly different at ($P \leq 0.05$).
A, B, C: Mean values with different superscript letters in the same column refer to different times within the same group are significantly different at ($P \leq 0.05$).

Table 2 Effect of tamoxifen and amygdalin administration on WBCs with its differential counts in DMBA-induced mammary carcinoma in female mice.

		WBCs ($\times10^3$/µL)	Neutrophils (%)	Lymphocytes (%)	Monocytes (%)	Eosinophiles (%)	Basophiles (%)
Control	2nd WK	5.00±0.35 ^{Ac}	28.67±0.88 ^{Ab}	60.67±1.45 ^{Ab}	5.67±0.33 ^{Ab}	2.67±0.33 ^{Aa}	0.00±0.00 ^{Ac}
	4th WK	5.04±0.34 ^{Abc}	28.70±0.86 ^{Aa}	60.69±1.41 ^{Ac}	5.70±0.31 ^{Aa}	2.68±0.31 ^{Aa}	0.00±0.00 ^{Ab}
DMBA	2nd WK	7.53±0.33 ^{Aab}	14.00±0.58 ^{Ac}	76.00±0.58 ^{Ba}	7.33±0.67 ^{Aa}	0.33±0.33 ^{Ab}	2.33±0.33 ^{Aa}
	4th WK	6.70±0.06 ^{Aa}	10.00±0.58 ^{Bc}	79.00±0.58 ^{Aa}	6.33±0.33 ^{Aa}	0.67±0.33 ^{Ab}	4.00±0.58 ^{Aa}
Tamoxifen	2nd WK	6.83±0.26 ^{Ab}	37.00±1.73 ^{Aa}	54.00±1.73 ^{Bc}	5.33±0.33 ^{Ab}	2.67±0.33 ^{Aa}	1.00±0.00 ^{Ab}
	4th WK	4.00±0.52 ^{Bc}	23.67±1.45 ^{Bb}	68.00±1.73 ^{Ab}	5.33±0.33 ^{Aab}	2.67±0.33 ^{Aa}	0.33±0.33 ^{Ab}
Amygdalin	2nd WK	8.43±0.55 ^{Aa}	35.00±1.73 ^{Aa}	56.33±2.03 ^{Bbc}	5.33±0.33 ^{Ab}	2.33±0.33 ^{Aa}	1.00±0.00 ^{Ab}
	4th WK	6.00±0.17 ^{Bab}	27.67±0.88 ^{Ba}	64.33±1.45 ^{Abc}	4.33±0.33 ^{Ab}	3.33±0.33 ^{Aa}	0.33±0.33 ^{Ab}
Tamoxifen + Amygdalin	2nd WK	7.93±0.15 ^{Aab}	36.67±0.88 ^{Aa}	54.00±1.15 ^{Bc}	6.00±0.58 ^{Aab}	2.33±0.33 ^{Aa}	1.00±0.00 ^{Ab}
	4th WK	5.73±0.38 ^{Bab}	31.00±1.15 ^{Ba}	61.33±1.76 ^{Ac}	5.33±0.33 ^{Aab}	2.33±0.33 ^{Aa}	0.00±0.00 ^{Ab}

Table 3 Effect of amygdalin and tamoxifen on mammary tissue oxidative stress and serum progesterone hormone concentration in DMBA-induced mammary carcinoma in female mice.

		MDA (mmol/g)	TAC (µm/g)	Progesterone (ng/ml)
Control	2nd WK	1173.17±12.87 ^{Ab}	1.86±0.03 ^{Aa}	3.05±0.10 ^{Ad}
	4th WK	1171.19±12. 89 ^{Ac}	1.88±0.04 ^{Aab}	3.03±0.13 ^{Ac}
DMBA	2nd WK	1309.25±91.80 ^{Bb}	1.82±0.02 ^{Aa}	6.14±0.04 ^{Ba}
	4th WK	2099.31±196.33 ^{Aa}	1.54±0.07 ^{Bb}	6.66±0.12 ^{Aa}
Tamoxifen	2nd WK	1746.47±191.59 ^{Aa}	1.58±0.11 ^{Aab}	3.97±0.15 ^{Ac}
	4th WK	1130.95±8.40 ^{Bc}	2.16±0.22 ^{Aa}	3.10±0.13 ^{Bc}
Amygdalin	2nd WK	2070.10±77.13 ^{Aa}	1.37±0.14 ^{Ab}	4.38±0.02 ^{Ab}
	4th WK	1557.14±69.34 ^{Bb}	1.61±0.01 ^{Ab}	3.64±0.16 ^{Bb}
Tamoxifen + Amygdalin	2nd WK	1372.03±109.71 ^{Ab}	1.74±0.02 ^{Aa}	4.02±0.05 ^{Ac}
	4th WK	1138.89±8.40 ^{Ac}	2.20±0.17 ^{Aa}	3.05±0.10 ^{Bc}

4. DISCUSSION

The purpose of this study was to evaluate the effects of tamoxifen and amygdalin on diminishing DMBA actions, as well as to compare the efficacy of these synthetic and natural medications with mammary tumor treatment over 4 weeks.

The obtained data showed that treatment of mammary cancer mice with amygdalin and tamoxifen for two-week and four-week intervals effectively restored all hematological parameters to the normal range, with the latter having a more potent effect than the former. Throughout the trial, Amygdalin was effective in raising Hb, RBCs, and HCT and in peripheral blood lymphocytes (PLTs) as reported in (Singh and Singh 2008). In other hand, tamoxifen treatment revealed a drop in hematological values after 2 and 4 weeks of administration. Similarly, (Grey et al., 1997) who found a decline in Hemoglobin (Hb), hematocrit (HCT), red blood cell count (RBCs), and WBC count after tamoxifen treatment. Mannucci et al. (1996) evaluated hemostatic factors in tamoxifen use; they showed that Hct, Hb, and platelet levels fell in the group treated with tamoxifen. However, the combined treatment of amygdalin with tamoxifen showed a significant improvement in complete blood counts. That matches with (Rhiouani et al., 2008) who stated the changes in hematological parameters owing to natural substances and medicines exposure as a consequence of treatment. Anemia is indicated by a decrease in Hb, RBC, and HCT (Pilny, 2008), that is matching with DMBA mice group. Therefore, intoxication can cause anemia due to alterations in erythropoiesis, the inhibition of hematopoietic organs' activity, or the accelerated breakdown of red blood cells (RBCs) due to changes in RBC membrane permeability (Yuan et al., 2014). Moreover, the obtained results showed a significant decrease in platelets count with DMBA, that may be resulted from the suppression of bone marrow activity, decreased synthesis, increased consumption, or excessive platelet aggregation (Sirag, 2009). When blood vessels are damaged, platelets play a key role in forming a plan to stop bleeding (Campbell and Ellis, 2007). Multiple mechanisms have been proposed to account for this phenomenon, such as an increase in the osmotic fragility of red blood cells or a decline in the health of bone marrow cells. It is worth noting that changes in hematological parameters may result from treatment-induced exposure to natural substances (Rhiouani et al., 2008).

According to Adebayo et al. (2010), a rise in white blood cells (WBCs) is a typical immune response to pathogens. White blood cell counts across the board (lymphocytes, monocytes, eosinophils, and basophils) revealed a significant increase in DMBA mice group as a result of cancer obtained (Riley and Rupert, 2015). Amygdalin and tamoxifen treatments for two-week and four-week intervals effectively revealed improvements on WBCs with its differential counts which were raised with carcinoma, that was in accordance with (Strati and Shanafelt, 2015).

Treatment with tamoxifen demonstrated highly improvement in progesterone level after 2 and 4 weeks, with the latter being the preferred duration. Considering that secretory changes were observed in endometrial specimens collected during therapy, it appears that tamoxifen has no deleterious influence on the endometrial response. There is a lack of data on how tamoxifen interacts with human steroid receptors. The upregulation and activation of estrogen and progesterone receptors in the endometrium were validated by Stendahl et al. (2006). According to research by Hefti et al. (2013), tamoxifen had no discernible effect on endometrial estrogen or progesterone receptor concentrations. However, in cases of breast or endometrial cancer, progesterone receptors were enhanced after brief tamoxifen treatment (Davies et al., 2011).

In contrast, this study found no appreciable differences in progesterone release due to amygdalin addition, but it did find that amygdalin blocked that hormone generated by carcinogenic DMBA throughout the experiment. Similar findings were observed by (Halenár et al., 2013a), who found no statistically significant alterations in the ovarian release of progesterone following amygdalin administration. Natural substances were found to have minimal effects on progesterone hormone in previous research on animal reproductive systems (Kolesárová et al., 2012a).

Furthermore, the current study showed that Amygdalin effectively controlled the antioxidant defense system throughout the experiment, especially after 4 weeks, by lowering L-malonedialdehyde (L-MDA) levels and regulating total antioxidant capacity (TAC) levels, both of which are indicative of Amygdalin's antioxidant properties and free radical scavenging capacity. Similarly, Karabulut et al., (2014) demonstrated that amygdalin supplementation offered robust protection against the oxidative stress generated by DMBA by lowering oxidative stress and MDA levels and raising TAC values. In a mouse model of 7,12-dimethylbenz [a] anthracene (DMBA)-induced carcinogenesis, the amygdalin-containing fraction showed anticancer efficacy in vivo by decreasing lipid peroxidation and boosting the antioxidant response as evaluated by total antioxidant capacity (TAC) and malondialdehyde (MDA). Amygdalin was found to play a role in the functioning of the amygdalin-containing fraction. The latter could be metabolized into HCN in malignant tissue, leading to cell death via oxidative stress (Hosny et al., 2021). Furthermore, in comparison to the DMBA carcinogenic group, after 4 weeks the therapeutic dose of tamoxifen increased TAC concentration and decreased MDA concentration. The findings of (Lim et al., 1992), who found that tamoxifen inhibits the production of hydrogen peroxide, corroborated these findings. Tamoxifen's antioxidative potential can be explained as follows. Tamoxifen is metabolized into 4-hydroxy tamoxifen and N-desmethyl tamoxifen by the cytochrome P450, a dependent oxidase, in the liver during tamoxifen mediation. 4-hydroxy tamoxifen, like estrogen, inhibits lipid peroxidation more effectively than its parent molecule. This antioxidant property of breaking chains and the possible impacts on membrane structure are a result of the phenolic hydroxyl group (Shapiro, 1991).

5. CONCLUSION

In conclusion, the combination of amygdalin and tamoxifen was found to be highly effective against mammary carcinoma. That reversed the dangerous effects of DMBA on antioxidant, progesterone hormone and hematological parameters and improved oxidative status of the mammary tissue in female mice. Therefore, we recommend combining tamoxifen with amygdaline as the model management for treating breast cancer.

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