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REVIEW ARTICLE

A review on breast cancer in Iraq and future therapies insights

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ABSTRACT

Cancer is one of the most common diseases around the world and the second leading cause of death after cardiovascular disease. Breast cancer is the most prevalent cancer type among Iraqi women, as it represents the highest percentage of malignant tumors in women until 2018. Therefore, women should be aware of the aggravation of this disease, the importance of the periodic examination for early detection for breast cancer, and following the most appropriate means for the treatment to get recovered and, thus, to reduce mortality. To fight cancer, there is an urgent need to search for new effective anticancer therapies that alter the molecular biology of tumor cells, stimulate the immune system, or specifically deliver chemotherapy factors directly to cancer cells without affecting normal cells and reducing the side effects of treatments. In this context, this paper aimed to highlight the therapeutic approaches used in the current researches of breast cancer treatment. Accumulated evidence showed that medicinal plants extracts, virotherapies, and nanomaterials can serve as anticancer agents. The proposed mechanisms were discussed and presented in this review.

Keywords alternative therapies, breast cancer, cancer cells, nanoparticles, virotherapy

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INTRODUCTION

Breast cancer is one of the malignant neoplasms and the most prevalent type of cancer among women all over the world. In 2015, 1.5 million cases of breast cancer were recorded, which is one in 4 new cases diagnosed worldwide (representing 25% of all cancer cases among women), and about 570,000 deaths worldwide.[1] In 2018, about two million new cases of breast cancer and about 626 deaths were recorded globally in 185 countries, according to the global cancer statistics, and breast cancer appeared to be the most popular in 154 out of 185 countries listed in "GLOBOCAN 2018" and also the breast cancer has highest rate. Breast cancer mortality among women (15%), then lung cancer (13.8%), colorectal cancer (9.5%), and cervical cancer (7.5%).[2,3] In the United States of America, approximately 276,480 women are diagnosed annually with breast cancer, which occupies

(30%) of the rest of the other cancers that affect women.[4] The breast cancer incidence rate in women is 100 times more than that of men.[5] Statistics indicate that the rate of breast cancer is more common and higher in the most developed countries, while the death rate from breast cancer is higher in the less developed countries.[6] In Iraq, breast cancer ranks first among malignant tumors among Iraqi women in general and the second main cause of death for women next to cardiovascular diseases.[7,8] Breast cancer rates in Iraq were generally stable from 2000 to 2009, but the latest statistics of the Iraqi Cancer Registry revealed a dangerous rise in incident rates that began after 2009, especially among women over 50 years old.[9] In 2013, breast cancer represented (19.4%) of all cancers diagnosed at that time, about (34.7%) of malignant tumors that afflicted women and (22.5%) of deaths among Iraqi women with cancer.[10] Studies in Iraq have indicated that the highest rates of breast cancer have been observed in a large proportion among middle-aged women, and that more than (40%) of cases are discovered in advanced stages of the disease.[11,12]

The last annual report of the Iraqi Cancer Registry released in 2018, that of the estimated population of 38 million, the total number of new cancer cases reached (31,502) cases. The total number of deaths due to cancer was (10,293) deaths. Table 1 shows that the highest incidence rate among the top 10 highly frequent cancers in Iraq was that of the breast cancer.

Table 1 **Distribution of cancersof higher incidence and mortality rates in Iraq (2018).**[13]

Higher incidence rate	No.	%	Higher mortality rate	No.	%
Breast	6,206	19.70	Bronchus and lung	1,628	15.82
Bronchus and lung	2,529	8.19	Breast	1,198	11.64
Colorectal	1,936	6.15	Leukemia	865	8.40
Leukemia	1,899	6.03	Brain and CNS	830	8.06
Urinary bladder	1,542	4.89	Colorectal	637	6.19
Brain and CNS	1,541	4.89	Stomach	554	5.38
Thyroid gland	1,413	4.49	Liver	535	5.20
Non-Hodgkin lymphoma	1,268	4.03	Pancreas	479	4.65
Skin and other	1,142	3.63	Urinary bladder	417	4.05
Prostate	1,023	3.25	Non-Hodgkin lymphoma	343	3.33
Total top 10	**20,549**	**65.23**	**Total top 10**	**7,486**	**72.73**
Total cancers of other sites	**10,953**	**34.77**	**Total cancers of other sites**	**2,807**	**27.27**
Total	**31,502**	**100**	**Total**	**10,293**	**100**

The breast cancer incidence is gradually increasing, and the total number of cases is 6,094 or (34.06% of all cancer types), while the number of deaths has reached 1,166 cases or (23.02% of all cancers). The highest death rate was among women in the age group of 70 years and over. Table 2 shows that the highest incidence rate and mortality of the top 10 highly frequent cancers in females were of breast cancer and the lowest was those of stomach and uterus unspecified cancer.

The bronchial and lung cancers ranked as cancers with the highest incidence rate among Iraqi men patients with total cases of 1,830 in 2018, and also the highest deaths rate among cancer patients are that of bronchial and lung cancers (22.30%). Table 3 shows the highest incidence and mortality rates of top 10 highly frequent cancers amomg Iraqi men.

Table 2 Distribution of cancersof higher incidence rate and mortality among Iraqi females (2018).[13]

Higher incidence rate	No.	%	Higher mortality rate	No.	%
Breast	6,094	34.06	Breast	1,166	23.02
Thyroid gland	1,097	6.13	Bronchus and lung	462	9.12
Colorectal	918	5.13	Leukemia	393	7.76
Leukemia	838	4.68	Brain and CNS	382	7.54
Bronchus and lung	749	4.19	Colorectal	292	5.77
Ovary	721	4,03	Liver	264	5.21
Brain and CNS	719	4.02	Stomach	255	5.03
Non-Hodgkin lymphoma	588	3.29	Ovary	208	4.11
Skin and other	558	3.12	Pancreas	198	3.91
Stomach	455	2.54	Uterus unspecified	184	3.63
Total top 10	**12,737**	**71.20**	**Total top 10**	**3,804**	**75.10**
Total cancers of other sites	**5,153**	**28.80**	**Total cancers of other sites**	**1,261**	**24.90**
Total	**17,890**	**100**	**Total**	**5,065**	**100**

Table 3 Distribution of cancers of higher incidence rate and mortality among Iraqi males (2018).[13]

Higher incidence rate	No.	%	Higher mortality rate	No.	%
Bronchus and lung	1,830	13.44	Bronchus and lung	1,166	22.30
Urinary bladder	1,173	8.62	Leukemia	472	9.03
Leukemia	1,061	7.79	Brain and CNS	448	8.57
Colorectal	1.023	7.52	Colorectal	335	6.60
Prostate	1,018	7.48	Prostate	326	6.24
Brain and CNS	820	6.02	Stomach	299	5.72
Non-Hodgkin lymphoma	680	5.00	Urinary bladder	291	5.57
Skin and other	584	4.29	Pancreas	281	5.37
Stomach	524	3.85	Liver	271	5.18
Pancreas	413	3.03	Non-Hodgkin lymphoma	201	3.84
Total top 10	**9,126**	**67.04**	**Total top 10**	**4,100**	**78.42**
Total cancers of other sites	**4,486**	**32.96**	**Total cancers of other sites**	**1,128**	**21.58**
Total	**13,612**	**100**	**Total**	**5,228**	**100**

According to the results of the above tables, this review aims particularly to highlight alternative therapeutic approaches that work against breast cancer. Additionally, we discussed the proposed mechanisms, which can be promising in the treatment of cancer.

BREAST CANCER

Breast cancer is a disease with heterogeneous characteristics. Clinically and based on cellular markers, it can be classified into three subtypes depending on the characteristics of gene expression: ER (estrogen receptor) an/or PR (progesterone receptor), HER2+ (breasts cancer with human epidermal growth factor receptor 2 positive), and TNBC (triple-negative

breast cancer).[14] About 70% of breast cancer cases are ER+ or PR+ and the HER2+ (also abbreviated as ERBB2+) can be seen in 15-20% of cases. All these receptors are proteins on the plasma membrane cells. The TNBC is about 15% of breast cancer cases and in this type, no proteins are on the surface of plasma membrane cells.[15] In addition, cancer stem cells (CSCs), a new subtype of malignant cells, related to tumor initiation and progression have been observed. These tiny nests of cells can be developed from stem or primogenitor cells within normal tissues, have self-renewal abilities and resistance to traditional therapies like radio- and chemotherapies.[16,17] Figure 1 shows the internal anatomy of the breast and tumor genesis, such as swelling can appear as a lump growing to be large enough to be detected.

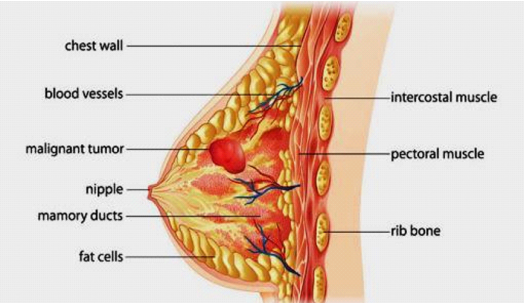

Figure 1 **Internal anatomy of the breast.**[18]

Risk factors

Tumors of breast generally begin from ductal hyper-proliferation, and progress to benign tumors or metastatic cancer by various carcinogens as a result of continuous stimulation. Tumor microenvironments, such as stromal influences, play important role in the initiation and progression of the breast cancer. The mammary gland can transformed into a tumor, when exposes stroma to carcinogens, and not the extracellular or the epitheliums.[19,20] Breast cancer remains one of the most common malignancies in women, as the incidence of it is increasing continuously all over the world. The number of women who suffer from this disease is still increasing, especially in those countries that previously had a relatively low rate of breast cancer because these countries nowadays adopt Western lifestyles for reproductive behavior.[21] The high incidence of breast cancer is closely related to genetics,[22] family history of breast cancer and environmental factors, behavioral habits, culture of knowledge, reproductive factors, menstruation at an early age, menopause, age of women at first birth and miscarriages.[23,24] In recent studies, many other factors have been focused on, including genetic predisposition, modern lifestyle, diet, obesity, alcohol consumption, smoking and childbearing at a later age for the first time.[25,26] It has also been shown that taking the contraceptive pill continuously increases the risk of breast cancer.[27] In Iraq, one study indicated that the positive risk factor for breast cancer was old age $\geq$60 years, menopausal age, divorced or widowed, age at menstruation <12 years, and continuous use of contraceptive pills for $\geq$1 year. A family history, second-degree relative, unrelated to

breast cancer. However, as regards marital status, when comparing the divorced or widow women with married, shown this relation was statistically significant.[28] It is important to conduct early and periodic examinations for women, especially if the disease is discovered early, to determine the appropriate treatment and reduce the mortality rate.

ALTERNATIVE THERAPIES FOR BREAST CANCER

Novel therapeutic approaches currently being developed to fight breast cancer include the use of plant extracts, viral therapy, and nanomaterials as anti-cancers.

Medicinal plants

Several studies have been conducted in Iraq that dealt with different plants to test the effect of their extracts on normal and cancerous cells, *in vivo* and *ex vivo*. Among these plants are the crude extracts of the *Cyperus rotundus*,[29] green tea,[30] sage leaves of *Salvia officinalis*[31] and *Nerium oleander*[32]. In addition, *Salix acmophylla*, which has an inhibitory effect on murine mammary adenocarcinoma (AMN3).[33] The anti-cancer effect of plant extracts of *Olea europea*[34] and *Urtica dioica*[35] on the growth of cancer cells (AMN3) have been reported with a significant inhibitory effect, and this can be attributed to their content of bioactive compounds (e.g. tannins, flavonoids, terpenes, phenols and vitamins) which have an anti-cancer effects. The kalgan plant and the crude extract of its grains has also showed an inhibitory effect on AMN3 cancer cells.[36] As well, the toxic effects of *Datura stramonium* extract have been reported to reduce tumor growth in mammary gland carcinomas,[37] and that of *Sonchus oleraceus* extract showed growth inhibitory effects on AMN3 cells.[38] The cytotoxic effect of the extract of *Zingeber officinale* rhizome on AMN3 growth has also revealed high inhibitory effects.[39] In addition, such effects of different raw extracts of *Daucus carota*, *Curcuma longa* and *Solanum melongena* have also been evidenced to have an effect on murine mammary adenocarcinoma cell line AMN3.[40] The leaf extract effect of *Plantago lanceolata* against different human breast cancer cell lines (AMJ13, MCF7, CAL51, and MDAMB) showed a selective inhibition on TNBS cells (CAL51) proliferation, while exhibited a slight effect on the other breast cancer cells.[41] Treating breast cancer cells (AMJ13) with 2-benzhydrylsulfinyl-n-hydroxyacetamide-Na extracted from fig fruit resulted in suppressing cancer cells proliferation, and then apoptosis.[42] The pros, most plant extract employed as anticancer agents such as Camptothecin derivatives, Paclitaxel, Topotecan and Irinotecan, in the treatment of some cancers inhibit mitotic cell via microtubule structure and topoisomerase I inhibition.[43] On the other hand, flavonoids can interact with the phosphorylation of cyclin-dependent kinases, arresting activation and restricting cell-cycle advancement at G1 or G2 phases.[44] The advantages of bioactive agents derived from plants are fewer side effects, eclectic targeting, less toxicity and no resistance to substances.[45] As for the cons, medicinal plants usually take longer as a therapy alone; it may

take 3 months for a trial to evaluate the results. Investigations into the dosage range of potentially beneficial products are needed, with cooperative studies to locate the long-range preventive profile.[46] Many plants were suggested as alternative approaches are facilely made and administered at home by the patient or a family member without the need of medical personnel. Also, the low or no toxic effects of these candidates make them easily usable. There are many kinds of research that are currently being conducted using different plant extracts which are all striving to find an appropriate treatment for breast cancer.

Virotherapies

In Iraq, the first trial of Newcastle disease virus (NDV) as a viral treatment against cancer cells was conducted by Al-Shammari (2003),[47] and later studies were conducted about 12 years later[48,49]. The proposed mechanism for these viruses as anti-cancers is that they multiply inside malignant cells and destroy them without affecting healthy cells, as they infect cancer cells by analyzing membranes and then entering or attaching to their receptors that emerge from the surfaces of the targeted cancer cells.[50] The oncolytic measles virus is another promising viral-based therapy for breast cancer cells in clinical trials. The study, which were conducted on two types of breast cancer cell lines one on an Iraqi woman (AMJ13) and the other on a Caucasian woman (MCF7), showed that this viral treatment has high effectiveness in killing breast cancer cells.[51] The glucose analog (2-deoxyglucose) was used as synergistic agent to increase the antitumor effectiveness of NDV against AMJ13 and AMN3 breast cancer cells. The results of synergistic cytotoxicity were revealed significant tumor growth inhibition by apoptotic cell death and GAPDH downregulation and inhibition to glycolysis product pyruvate.[52] Attenuated oncolytic measles virus is considered a useful vaccine and safe anti-cancer treatment through its clear effect on AMJ13 cells.[53] In addition, one of the recent studies conducted in Iraq confirmed that the NDV is an antitumor agent because it showed a clear effect in inhibiting the growth of AMN3 (mouse breast cancer cells), and it is also suggested as a live vaccine.[54] The advantages of viral therapy are that the oncolytic vectors have the ability to bind perfectly to the cell, enter the tumor cell by receptor-mediated endocytosis easily, proliferate in cancer cells selectively as opposed to normal cells, and have minimal side effects. Each way of administration has several disadvantages according to dosage, specificity, complexity, efficiency, and feasibility. All these must be carefully studied in order to achieve optimal delivery with the least possible adverse effects.[55] However, more research and continued efforts are still needed to reduce impacts and achieve delivery efficiency.

Nanotherapies

Nowadays, the use of therapeutic nanomaterials, particularly metal nanoparticles, in medicine is increasing because of their new and different characteristics that are promising

if they applied in various fields of biomedicine.[56] Nanoparticles can effectivley be used in the detection of cancer and its therapy with lower side effects on normal cells.[57] In Iraq, many studies were conducted on the use of different types of metallic nanoparticles to target the breast cancer, and part of these researches and studies were done at the Iraqi Center for Cancer Research and Medical Genetics (Al-Mustansiriya University, Baghdad, Iraq). The AMN3 breast cancer cells have been exposed to several types of nanoparticles as primary treatments, and they have shown a high ability to kill cancer cells. Among these nanomaterials, zinc oxide nanoparticles (ZnONPs),[58] gold nanoparticles (AuNPs)[59] and silver nanoparticles (AgNPs)[60]. AgNPs showed a significant influence against AMJ13 breast cancer cells for an Iraqi woman, and the investigations at the cellular and molecular levels showed the ability of these materials to cause high cytotoxicity, breakdown of DNA, and a decrease in the level of glutathione (antioxidant) and induce cells to apoptosis.[61] The AuNPs have also shown a notable role as an anti-cancer agent (MCF7 breast cancer cells) through their toxic effect on these cells, and the results of the study conducted by Ali and colleagues (2019), in this respect, confirmed the possibility of using AuNPs in wide medical applications in the future and the possibility of introducing them as a new approach instead of chemotherapy in the treatment of different types of cancer diseases.[62] Sulaiman et al. (2018)[63] have observed that the magnetic iron oxide nanoparticles (MNPs) are able to induce cytotoxic influence towards both human breast cancer cells (AMJ13 and MCF7) via inducing apoptosis. Regarding the advantages of nanoparticles, they are began to be used as a new and promising treatment system. This may help to get over different limitations of traditional therapies such as side effects, treatment resistance, delayed response, etc. The radiotherapy by using metallic nanoparticles gives additional advantage that metallic nanoparticles eclectically shatter and/or absorb high-energy X-rays or Y-rays. This improves the targeting of cellular components within the tumor tissue, and thus leads to more local damage desirable in such therapies.[64] However, the disadvantages of nanomaterials may include their cellular uptakes, long-term potential material toxicity and its excretion mechanisms.[65]

Table 4 elucidates the suggested therapeutic approaches presented in this review and their mechanisms of action through which they can fight cancerous cells.

CONCLUSION

There are many factors that contribute individually or jointly to the emergence of breast cancer, especially in women who have a genetic predisposition to this disease or who come in contact with high-risk factors. Nowadays researchers' goal is to develop new treatments and conduct more researches to discover and develop effective medicines against breast cancer that are safe, have fewer side effects on the body, more efficient, and are less costly. Optimal therapy for each patient depends on tumor type, anatomic cancer stage, and patient state. However, and based on the available literature, the medicinal plants' extracts, virotherapies, and nanomaterials can serve as good candidates and future ther-

Table 4 **Suggested anti-cancer/anti-tumor agents and their mechanism in fighting cancer cells .**

Therapy	Killing mechanism	Source
Medicinal plants	• Growth inhibition • Cytotoxicity • Apoptotic cell death • High ROS level	39,42
Virotherapies	• Growth inhibition • Multiply inside cells and destroy by analyzing membranes • Apoptotic cell death • Necrosis • Pyroptosis • Autophagy • GAPDH downregulation • Inhibition to glycolysis product pyruvate • Breakdown of DNA • As vaccines	50,52
Nanotherapies	• Growth inhibition • Cytotoxicity • Breakdown of DNA • Decrease of glutathione level • Induce cells to apoptosis	61,63

GAPDH, *glyceraldehyde-3-phosphate dehydrogenase;* ***ROS,*** *reactive oxygen species*

apeutic approaches for breast cancer.

LIST OF ABBREVIATIONS

AgNPs, silver nanoparticles; **AMJ13**, human breast cancer cell lines; **AMN3**, murine mammary adenocarcinoma; **AuNPs**, gold nanoparticles; **CAL51**, human breast cancer cell lines; **CSCs**, cancer stem cells; **DNA**, deoxyribonucleic acid; **ER**, estrogen receptor; **G1**, Gap 1/Mitosis; **G2**, Gap 2/Mitosis; **GAPDH**, glyceraldehyde-3-phosphate dehydrogenase; **HER2+**, human epidermal growth factor receptor 2 positive; **MCF7**, human breast cancer cell lines; **MDAMB**, human breast cancer cell lines; **MNPs**, magnetic iron oxide nanoparticles; **NDV**, Newcastle Disease Virus; **PR**, progesterone receptor; **ROS**, reactive oxygen species; **TNBC**, triple-negative breast cancer; **ZnONPs**, zinc oxide nanoparticles.

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DECLARATIONS

Conflict of interest

The author has no conflict of interest.

Ethical approvals

Not applicable.

Data availability

Not applicable.

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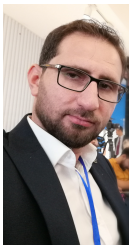

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