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Review

The Role of Glucosamine in the Treatment of Breast Cancer: A Systematic Review

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ABSTRACT

Backgrounds: Breast cancer is a common and multifactorial disease influenced by genetic, environmental, and lifestyle factors. Recent studies suggest that N-acetyl-D-glucosamine (D-GlcNAc) may have anti-tumor effects, particularly through its binding to HER-2 receptors in breast cancer cells. This systematic review aims to investigate the role of glucosamine in the treatment of breast cancer.
Methods: A comprehensive literature search from 2000 to July 2025, adhering PRISMA guidelines, was conducted through five databases PubMed, Scopus, Web of Science, Science Direct, and Google Scholar. After screening full-text articles, nine studies were included in this systematic review. Due to heterogeneity among studies, a qualitative and quantitative synthesis was performed.
Results: The literature review revealed mixed findings on the relationship between glucosamine intake and cancer risk, with some studies indicating a potential protective effect, particularly against breast cancer, through mechanisms like apoptosis, glycosylation, and inflammation modulation. However, inconsistencies in study designs and results precluded definitive conclusions. Further research is required to confirm glucosamine's role in breast cancer prevention and treatment.
Conclusion: This review suggests that glucosamine may have protective effects against breast cancer through anti-inflammatory and cellular mechanisms. However, inconsistencies in study designs highlight the need for further large-scale research. Understanding glucosamine's role in cancer prevention could lead to new therapeutic approaches.

Keywords: Glucosamine, Breast cancer, Risk factors, Systematic review, Cohort study

Introduction

Breast cancer is a disease that will affect 1 in 8 women during their lifetime, and represents the second most common cancer diagnosed in women [1]. In 2022, there were 2.3 million women diagnosed with breast cancer and 670,000 deaths globally. Breast cancer occurs in every country of the world in women at any age after puberty but with increasing rates in later life [2]. In Iran, the incidence of BC in women is rising precipitously, accounting for 28.1% of female malignancies. Substantial regional variations have been observed in this country, with markedly high incidence rates documented in Isfahan and Yazd provinces [3]. BC can be diagnosed through mammography, specialized X-ray scans, or by finding an abnormal mass in the breast tissue, either by the patient or their doctor [4]. Many risk factors contribute to the development of BC, including early

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menstruation, late menopause, marriage at an older age, use of contraceptives, breastfeeding, inactivity and obesity, family history, history of radiation exposure, and alcohol and tobacco use [5]. Breast cancer risk is related to both endogenous and exogenous estrogen. In premenopausal women, the ovary produces endogenous estrogen, and its removal can lower the risk of breast cancer. The main exogenous sources of estrogen are HRT and oral contraceptives. According to several studies, the use of HRT can raise the risk of breast cancer [6]. Additionally, large breast size, personal history of breast cancer [8], overweight or obesity [9], late menopause [10], and exposure to estrogen (both endogenous and exogenous) have been identified as risk factors [11]. Breast cancer is a metastatic cancer and can commonly transfer to distant organs such as the bone, liver, lung, and brain, which mainly accounts for its incurability [4, 7]. Based on both molecular and histological evidence, BC could be categorized into three groups; BC expressing hormone receptor (estrogen receptor (ER+) or progesterone receptor (PR+)), BC expressing human epidermal receptor 2 (HER2+), and triple-negative breast cancer (TNBC) (ER−, PR−, HER2−).(8, 9)The treatment approaches should be based on the BC molecular characteristics. In addition, the TNBC is divided into six categories; basal-like 1 (BL-1), basal-like 2 (BL-2), immunomodulatory (IM), mesenchymal (M), mesenchymal stem cell-like (MSL), and luminal androgen receptor (LAR) [10]. High efflux of anticancer agents that is accomplished by ATP-binding cassette (ABC) transporters such as human breast cancer resistance protein (BCRP/ABCG2) leads to reduced intracellular drug concentration and has been considered to be the main reason for drug resistance [11].

Different agents have been developed to overcome ABC transporter-mediated drug efflux, but the choices with minimal adverse effects remain limited [12, 13].

Glucosamine (GlcN), 2-amino-2-deoxy-D-glucose, is a naturally occurring sugar found in the human body. Glucosamine is a precursor of various substances that are involved in building tendons, ligaments, cartilage, and synovial fluid [14]. Glucosamine is a non-mineral and non-vitamin supplement. Additionally, glucosamine can regulate various signaling pathways and play a pharmacological role in multiple diseases, including skin diseases, cancer, bacterial infections, and cardiovascular diseases [15]. Although there are few studies considering the effects of glucosamine on breast cancer, a study conducted in 2024 demonstrated the positive effect of D-GlcNAc administration on breast cancer cells, leading to increased apoptosis in the malignant phenotype. The binding affinity of N-acetyl-D-glucosamine (D-GlcNAc) to HER2 receptors suggests a potential mechanism of action. These results contribute to understanding D-GlcNAc as an anti-tumor agent for breast cancer treatment [16]. Additionally, GlcN enhanced the sensitivity of tumor cells to the apoptotic effect of doxorubicin through inhibition of transglutaminase 2 (TGase2) and NF-κB activities [17]. Investigations to find innovative treatment methods with fewer side effects continue to develop, and N-acetyl-D-glucosamine (D-GlcNAc) appears to be one [12].

The positive effects of D-GlcNAc on breast cancer cells need further large-scale studies and investigations. It is important to understand the role and the mechanisms of glucosamine in breast cancer treatment. Therefore, the objective of the following systematic review is to explore the effect of glucosamine in the treatment of breast cancer.

Methods

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [18])

Literature search

A comprehensive literature search was conducted to identify studies published between 2000 and 20 July 2025 that investigated the effect of glucosamine in the treatment of breast cancer. Electronic databases, including PubMed, were searched using relevant keywords such as “glucosamine,” “breast cancer,” “cancer,” “meta-analysis,” “systematic review,” and “ clinical trial (See Table 1). The search strategy was designed to retrieve all relevant articles, including randomized controlled trials, cohort studies, case-control studies, and cross-sectional studies. Titles and abstracts were screened for relevance, and full texts of potentially eligible articles were reviewed in detail. Two independent reviewers conducted data extraction and quality assessment, with any discrepancies resolved through discussion or consultation with a third reviewer. The EndNote X7 software (Thomson Research Soft, Philadelphia, PA) was used to import all the relevant articles. Duplicate studies were deleted.

Inclusion and exclusion criteria

After initial screening of abstracts to exclude irrelevant studies, full-text articles were assessed for eligibility based on the following criteria: availability in full text, written in English, providing detailed information on the effect of glucosamine in the treatment of breast cancer, and meeting the inclusion criteria. Duplicate studies and those that did not meet the inclusion criteria were excluded.

Data extraction

Two independent reviewers conducted data extraction using a standardized data extraction form. The extracted data included general characteristics of the study (first author, year of publication, study design) and the primary outcomes related to the association between glucosamine intake and breast cancer risk. Any discrepancies between the two reviewers were resolved through discussion and consensus.

Statistical analysis

The main strategy in the analysis was data synthesis. The heterogeneity of the included studies in terms of the study methods and outcome measurements hampered the possibility of a meta-analysis. Therefore, the results were presented as qualitative and quantitative syntheses according to the type of the study.

Results

Study Selection

In the initial search, 50 publications were found in total. After removing the duplicates and excluding the publications after title/ abstract review based on our eligibility criteria, 50 articles remained for full-text review. 28 of the 50 articles were excluded because of irrelevant study design and/or outcome. So finally, 22 studies [14, 17, 19-38] were identified for inclusion (Figure 1).

Study Characteristics

this systematic review focuses on the role of glucosamine in breast cancer treatment. Table 2 summarizes the key characteristics of the studies included in the review. Each row represents a different study, while the columns provide information such as the author and year, study design, sample size, glucosamine dosage and formulation, treatment duration, and the outcomes measured in relation to breast cancer treatment.

Description of the Outcomes

The study measured various in vitro and in vivo outcomes related to tumor inhibition, cell viability, and treatment efficacy. In vitro experiments included short-term and long-term treatments, with analyses such as flow cytometry, mRNA expression, apoptosis, cell cycle changes, and protein expression (e.g., STAT3, Bcl-2). Additionally, cellular uptake, cytotoxicity, and antitumor efficacy were evaluated using assays like MTT and BRET. In vivo studies monitored tumor size, osteocyte lesion area, weight loss, and biodistribution in mice, utilizing tools such as scintigraphy imaging and proteomic profiling. Patient pain reports and in-person interviews were also gathered for real-world clinical insight. Overall, the study employed diverse methods to assess tumor progression, drug efficacy, and cellular responses.

Results of the Outcome

Arcaro, K. F., et al. (2004) [19] Conducted how the disruption of surface carbohydrates on membrane receptors affects the development of foci in MCF-7 breast cancer cell cultures. The authors found that treatment with beta-galactosidase at concentrations of 0.013-0.05 units/ml completely inhibited foci development without damaging the monolayer of cells. Alpha-mannosidase had a similar but weaker effect. Using lectin-fluorescent conjugates (RCA and ConA), they identified surface carbohydrates on the cells. Co-treatment with galactose or lactose inhibited RCA binding, while mannose and N-acetyl-glucosamine reduced ConA binding. This is the first reported inhibition of foci formation via surface carbohydrate disruption on these cells.

Yang, D., et al. (2004) [20] conducted the use of 99mTc-EC-DG, a radiolabeled glucosamine analog, for assessing tumor response to therapy. In vitro assays showed that 99mTc-EC-DG could assess cell nuclei activity. In vivo, imaging in mice, rabbits, and rats demonstrated successful tumor visualization using 99mTc-EC-DG. Tumor/muscle

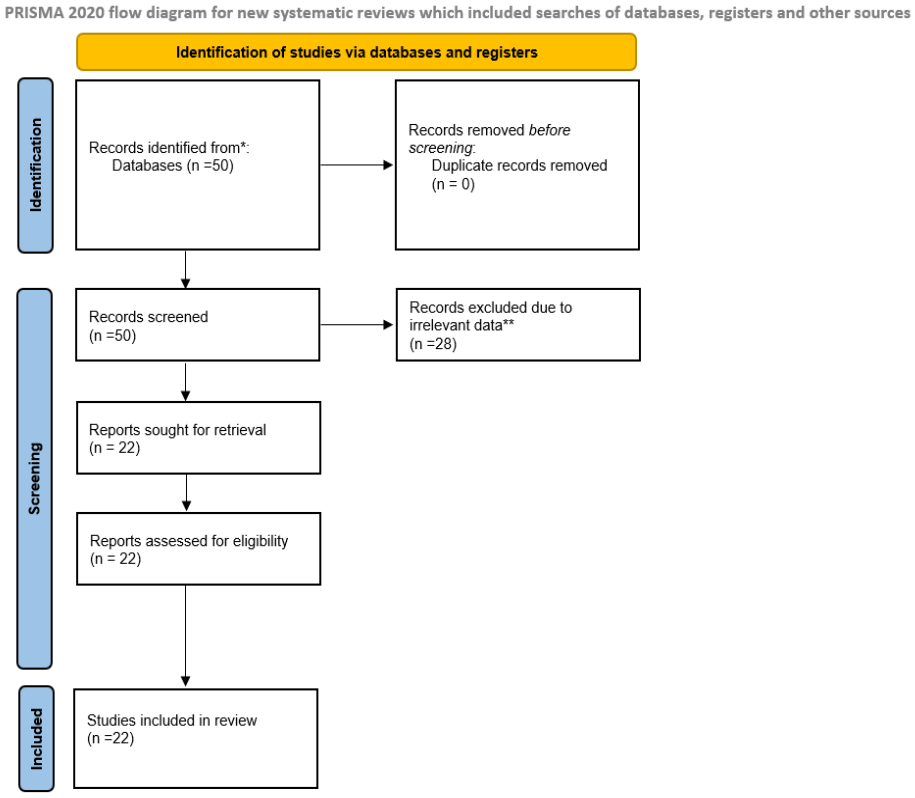

Figure 1.
Diagram illustrating the studies that were included, detailing the processes of identification, screening, eligibility assessment, and the final sample selection.

Table 1.
Keywords and search strategy

Database	Date	Keywords	Results
PubMed	10-Oct-24	"glucosamine"[Title/Abstract]	15,751
		((treatment[Title/Abstract]) OR ("Therapeutics"[Mesh] OR "therapy" [Subheading])) OR (("therapy"[Title/Abstract]) OR (therapeutics[Title/Abstract]))	13,474,881
		(Breast Cancer[Title/Abstract]) OR ("Breast Neoplasms"[Mesh])	470,645
		(("glucosamine"[Title/Abstract]) AND (((treatment[Title/Abstract]) OR ("Therapeutics"[Mesh] OR "therapy" [Subheading])) OR (("therapy"[Title/Abstract]) OR (therapeutics[Title/Abstract])))) AND ((Breast Cancer[Title/Abstract]) OR ("Breast Neoplasms"[Mesh]))	50

ratios derived from 99mTc-EC-DG scintigraphy could assess the efficacy of paclitaxel and cisplatin treatment in rodent models. Immunohistochemically analysis correlated the imaging findings with reduced bFGF expression, increased apoptosis, and cell cycle changes in the tumors after treatment.

Presant, C. A., et al. (2007) [21] conducted frequency and characteristics of pain associated with aromatase inhibitors, a common treatment for hormone-receptor-positive breast cancer. The study found that pain (arthralgia and/or bone pain) was reported in 61% of patients receiving aromatase inhibitors in a clinical setting. This is higher than the frequency typically reported in clinical trials, potentially due to differences in pain assessment and patient selection.

Xiong, Q. F., et al. (2007) [22] conducted the ability of 188Re-DTPA-DG, a radiolabeled glucosamine derivative, to induce apoptosis in MCF-7 breast cancer cells and A549 lung cancer cells. Flow cytometry analysis revealed that 188Re-DTPA-DG induced significant changes in cell nuclear morphology indicative of apoptosis, with a more pronounced effect than 188ReO4- (perrhenate). Biodistribution studies in tumor-bearing mice confirmed the preferential accumulation of 188Re-DTPA-DG in tumor tissue compared to normal tissue.

Greenlee, H., et al. (2009) [23] conducted the use of complementary and alternative medicine (CAM) among women with breast cancer. It mentions glucosamine as one of the CAM therapies used but doesn't focus specifically on its effects. The key finding is the high prevalence of CAM use (96.5% of participants) before diagnosis and (86.1%) after diagnosis.

Kim, D. S., et al. (2009) [17] studied the potential of curcumin as a chemo-preventive agent for breast cancer and explored the underlying mechanisms. While it doesn't directly involve glucosamine, it focuses on similar pathways relevant to cancer cell signaling and survival.

Paraskar, A., et al. (2012) [24]. This study investigated the efficacy and safety of a rationally designed oxaliplatin nanoparticle (PIMA–GA–DACH–platinum) for enhanced antitumor activity. The nanoparticle was formed by complexation between DACH-platinum and PIMA-GA copolymer. In vitro studies showed increased cellular uptake and cytotoxicity of the nanoparticle in various cancer cell lines, including 4T1, CP20, MDA-MB-231, and SKOV3. In vivo experiments using a 4T1 tumor-bearing mouse model demonstrated superior tumor growth inhibition by the nanoparticle compared to free oxaliplatin, with reduced systemic toxicity. Histological analysis revealed increased tumor apoptosis and minimal renal toxicity associated with nanoparticle treatment.

Pollari, S., et al. (2012) [25] This research investigated the role of heparin-like compounds, fragmin and K5-NSOS, in inhibiting breast cancer-induced osteolysis and tumor growth in bone. Using an in vitro model of MDA-MB-231 (SA) cells, the study identified that these compounds reduced TGF-β-induced IL-11 production. In vivo experiments using a mouse model of breast cancer bone metastasis showed that both fragmin and K5-NSOS significantly reduced osteolytic lesion area and tumor growth in bone. While fragmin did not significantly affect osteoclast activity in human osteoclast cultures, K5-NSOS exhibited a dose-dependent inhibition of osteoclast resorption activity.

Kanwal, S., et al. (2013) [26] his study examined the impact of O-GlcNAcylation on tamoxifen sensitivity in MCF-7 breast cancer cells. Increasing O-GlcNAcylation levels using PUGNAc and glucosamine protected MCF-7 cells from tamoxifen-induced cell death. This protective effect was associated with a reduction in estrogen receptor α (ERα) expression. Further investigations revealed that O-GlcNAcylation did not interfere with the IGF-1 signaling pathway in these cells. The results suggest that elevated O-GlcNAcylation levels may contribute to tamoxifen resistance by downregulating ERα expression.

Hosea, R., et al. (2018) [31] Glucosamine treatment decreased ALDH+ breast CSC viability in a dose-dependent manner, with significant reductions observed at concentrations ranging from 0.25 to 16 mM. At a concentration of 4 mM, glucosamine significantly downregulated the expression of stemness genes ALDH1A1 (0.7-fold; $P<0.05$), OCT-4 (0.46-fold; $P<0.01$), and KLF4 (0.42-fold; $P<0.01$) in ALDH+ breast CSCs. The number of mammospheres formed by untreated ALDH+ breast CSCs was 5.02-fold higher compared to MCF7 cells, indicating increased tumorigenicity. Treatment with 4 mM glucosamine significantly decreased the number of mammosphere-forming units (MFUs) in both ALDH+ breast CSCs and MCF7 cells. Glucosamine inhibited STAT3 phosphorylation in ALDH+ breast CSCs and MCF7 cells, with a less significant inhibition observed in ALDH+ breast CSCs ($P<0.05$) compared to MCF7 cells ($P<0.01$) at 4 mM glucosamine

Baysal, Ö., et al. (2024) [37] Treatment with 2 mM and

Table 2.
Data Extraction Table of all studies included in the systematic review.

No.	Author, date	Study design	Sample Characteristics [Sample size (n), age, gender	Intervention/ dosage	dose	Duration/ Follow-up	Outcome Measurements	Main outcome
1	Arcaro, K. F., et al. (2004) [19]	In vitro study	Not specified	Treatment with beta-galactosidase and alpha-mannosidase	Beta-galactosidase: 0.013-0.05 units/ml.	Not specified	Inhibition of foci development	Disruption of terminal sugars on membrane receptors using beta-galactosidase and alpha-mannosidase inhibits foci development in MCF-7 cell cultures.
2	Chou, W. Y., et al. (2015). [27]	In vivo In vitro	In Vitro: The study uses two human breast cancer cell lines: MCF-7 and MDA-MB-231. It doesn't specify the age or gender of the source of these cell lines. In Vivo: The animal model uses female athymic nude mice. The mice are 5 weeks old at the beginning of the acclimatization period.	Control groups: In well-designed experiments, the effects of an intervention are compared to a control group that does not receive the intervention. In this study, control groups include cells not exposed to glucosamine or mice receiving saline injections instead of glucosamine. Purpose of interventions: Interventions are essential for establishing cause-and-effect relationships. By manipulating the intervention and observing the resulting outcomes ,researchers can conclude the intervention's impact.Multiple interventions: Some studies involve multiple interventions or combinations of treatments. This allows researchers to explore the potential synergistic or antagonistic effects of different interventions.	In Vitro: MCF-7 cells are treated with glucosamine hydrochloride at concentrations of 0.01, 0.1, 1, and 10 mM. MDA-MB-231 cells are also treated with glucosamine at 1 and 10 mM. The PKC activator TPA is used at a concentration of 20 ng/ml to induce COX-2 and IL-8 expression. Various other inhibitors and stimulators are used to investigate specific signaling pathways, as detailed in the "Key Materials" section of my previous response. In Vivo: In the mouse xenograft model, 10 µl of a 100 mM glucosamine solution is injected intratumorally three times per week for five weeks.	In Vitro: Treatment durations vary depending on the specific experiment. Some treatments are short-term (e.g., 2 hours for pre-treatment with glucosamine), while others are longer (e.g., 24 hours for TPA exposure). In Vivo: Mice are monitored for eight weeks after tumor cell injection. Glucosamine treatment begins when tumors reach approximately 50 mm3, around three weeks after injection, and continues for five weeks. Tumor size is measured weekly throughout the study.	In Vitro: Treatment durations vary depending on the specific experiment. Some treatments are short-term (e.g., 2 hours for pre-treatment with glucosamine), while others are longer (e.g., 24 hours for TPA exposure). In Vivo: Mice are monitored for eight weeks after tumor cell injection. Glu cosamine treatment begins when tumors reach approximately 50 mm3, around three weeks after injection, and continues for five weeks. Tumor size is measured weekly throughout the study.	The primary finding is that glucosamine demonstrates anti-inflammatory and anti-tumor effects in both the in vitro and in vivo settings. Specifically, glucosamine reduces: ○COX-2 and IL-8 expression in MCF-7 breast cancer cells. ○PGE2 and IL-8 production. ○PKC-induced cell proliferation and migration. ○Tumor size and weight in the xenograft mouse model.
3	Yang, D., et al. (2 0 0 4) . [20]	In vitro and invivo study	Lung and breast cancer cells; nude mice; rabbits	Injection of 99mTc-EC-DG; treatment with paclitaxel and cisplatin	99mTc-EC-DG Kit Components: EC-DG (ethylenedicysteine-glucosamine): Typically 5 mg per kit for in vivo studies. Tin (II) chloride (SnCl2): 100 mg per kit. Gluconate (transchelator): Added at 20% w/w of EC-DG, resulting in 1 mg per kit. Radioactivity: Injected activity for mice: 1-2 mCi (37-74 MBq) per mouse. Injected activity for rabbits: 1 mCi (37 MBq) per rabbit. Injected activity for rats: 300 mCi (11.1 GBq) per rat.	0.5-4 hours for biodistribution in mice; varied for treatment studies	Scintigraphic imaging; immunohistochemical assays mRNA expression, apoptosis, and cell-cycle changes in tumor); flow cytometry analysis	99mTc-EC-DG is involved in cell nuclei activity and could assess the therapeutic tumor response.
4	Presant, C. A., et al. (2007). [21]	Interview study	56 patients with breast cancer, not on clinical trials	Treatment with aromatase inhibitors	While this study doesn't specify doses of aromatase inhibitors, it mentions that glucosamine was used as an effective therapy for controlling pain in 15% of patients.	Not specified	Patient reports of pain occurrence, character, severity, and resolution	Aromatase inhibitor-associated pain is more frequent in patients not in clinical trials than previously appreciated in clinical trials.

Continued Table 2.

No.	Author, date	Study design	Sample Characteristics [Sample size (n), age, gender	Intervention/ dosage	dose	Duration/ Follow-up	Outcome Measurements	Main outcome
5	Xiong, Q. F., et al. (2007). [22]	In vitro and in vivo study	MCF-7 breast carcinoma and A549 pulmonary carcinoma cells; breast tumor-bearing nude mice	Exposure to 188Re-DTPA-DG, 188Re-perrhenate (188ReO4-), and saline	Tested at radioactivity levels of 37, 55.5, or 74 kBq/mL.	18 hours for in vitro study; not specified for biodistribution study	Flow cytometry; biodistribution in nude mice	188Re-DTPA-DG has a significant apoptotic effect on carcinoma cells and is an effective radiopharmaceutical for intratumoral radiation therapy.
6	Greenlee, H., et al. (2009). [23]	Prospective cohort study	1,000 women with breast cancer	Various complementary and alternative medicine (CAM) therapies including green tea, glucosamine, and omega-3 fatty acids	While it mentions that glucosamine was among the CAM therapies used at least weekly by over 20% of women in the 5 years before diagnosis, it doesn't provide specific doses.	5 years before diagnosis and the period immediately following diagnosis	In-person interviews	CAM use is high before and after breast cancer diagnosis. Clinicians should discuss CAM use with breast cancer patients.
7	Kim, D. S., et al. (2009). [17]	In vitro study	Not specified	Treatment with glucosamine	not mentioned	Not specified	Cell death; I-kappaBalpha depletion; NF-kappaB activity	Glucosamine is a TGase 2 inhibitor and might be an attractive novel target for the treatment of malignant cancers.
8	Paraskar, A., et al. (2012). [24]	In vitro and in vivo study	Sample: The study used 4-8 mice per treatment group for the tumor volume and body weight analysis and 3-5 mice per group for the biodistribution study. The analysis of kidney weight as a marker for nephrotoxicity used 4-6 mice per group.Age: The mice used in the study were 4 weeks old at the time of tumor implantation.	Treatment with oxaliplatin and PIMA-GA-DACH-platinum nanoparticles	Administered at a dose equivalent to 5 mg/kg platinum	the duration of the follow-up period in the study was 6 days	In vitro efficacy; in vivo tumor inhibition; nephrotoxicity; body weight loss; biodistribution using inductively coupled plasma atomic absorption spectroscopy	The rational engineering of a novel polymeric nanoparticle inspired by the bioactivation of oxaliplatin results in increased antitumor potency with reduced systemic toxicity.
9	Pollari, S., et al. (2012). [25]	In vitro and in vivo study	MDA-MB-231(SA) breast cancer cells; athymic nude mice	Treatment with Fragmin, K5-NSOS, or vehicle; inoculation with MDA-MB-231 (SA) cells	Heparin, Fragmin, and K5-NSOS: All three were used at a concentration of 0.25 mg/mL.TGF-b: This was added at a concentration of 5 ng/mL. Smad Luciferase Reporter Assays: siRNAs were used at a concentration of 10 nmol/L alongside 93 ng of the luciferase reporter construct. They also used 5 ng/mL of TGF-b. Fragmin: Administered subcutaneously at 5 mg/kg daily. K5-NSOS: Administered intravenously at 5 mg/kg daily.	4 weeks	Weight; osteolytic lesion area; tumor burden in bone	Heparin-like glycosaminoglycans inhibit weight reduc tion, decrease osteolytic lesion area, and reduce tumor burden in bone. K5-NSOS is a potential antimetastatic agent.
10	Kanwal, S., et al. (2013). [26]	In vitro study	MCF-7 cells	Treatment with PUGNAc and/or glucosamine; inhibition of OGT expression by siRNA; treatment with tamoxifen	The study used PUGNAc, an inhibitor of OGA, and glucosamine (GlcN), which bypasses the GFAT rate-limiting step, to increase O-GlcNAcylation of proteins in MCF-7 cells. The specific concentrations used were 100 µM for PUGNAc and 5 mM for glucosamine.		Cell death; PIP3 production using BRET; Akt phosphorylation; ERα mRNA and protein expression	O-GlcNAcylation-inducing treatments protect MCF-7 cells from tamoxifen-induced cell death. Inhibition of O-GlcNAcylation may improve the sensitivity of breast cancer to tamoxifen.
11	Hosea, R., et al. (2018). [31]	In vitro study	Human ALDH (+) breast cancer stem cells and MCF7 cells	Treatment with glucosamine	varying concentrations of D-glucosamine hydrochloride (0.25, 1, or 4 mM) for 24 hours	24 hours	Cell viability; pluripotency gene expression (ALDH1A1, OCT-4, and KLF4); STAT3 and pSTAT3 levels; number of mammosphere-forming units (MFUs)	The results of the present study indicated that glucosamine treatment may be an improved approach to target the stemness of CSCs.

Continued Table 2.

No.	Author, date	Study design	Sample Characteristics [Sample size (n), age, gender	Intervention/ dosage	dose	Duration/ Follow-up	Outcome Measurements	Main outcome
12	Baysal, Ö., et al. (2024). [37]	In vitro study	Human ALDH (+) breast cancer stem cells and MCF7 cells	Treatment with glucosamine		24 hours	Cell viability; pluripotency gene expression (ALDH1A1, OCT-4, and KLF4); STAT3 and pSTAT3 levels; number of mammosphere-forming units (MFUs)	These findings c ontribute to understanding D-GlcNAc as a potential anti-tumor agent for breast cancer treatment.
13	Woodman, J. L., et al. (2015). [28]	In vitro and in vivo study	CD44(+)/CD24(-/low) human breast cancer cells (BT-474EMT)	Treatment with nCaP (CMHA) CDDP	Cis-diamminedi-chloroplatinum (II) (CDDP) loaded in CMHA-stabilized nanoparticles (nCaP (CMHA)CDDP): Tested at a dose of 7 mg/kg CDDP.	7 days for in vitro release study; Not specified for in vivo study	Release of CDDP; surface plasmon resonance; cellular uptake; cytotoxicity; tumor inhibition	CMHA-stabilized nanoparticles loaded with CDDP exhibit cytotoxicity against breast cancer cells in vitro but limited distribution in vivo.
14	Alshaker, H., et al. (2017). [29]	In vitro and in vivo study	Triple-negative breast cancer cells; mouse breast can cer models	Treatment with docetaxel, FTY720, and glucosamine; encapsulation in PLGA complex nanoparticles (CNPs)	DTX: 5 mg/kg FTY: 3 mg/kg Combined DTX + FTY: 5 mg/kg DTX + 3 mg/kg FTY CNP1: contained 5 mg/kg DTX + 3 mg/kg FTY CNP2: contained 2 mg/kg DTX + 2 mg/kg FTY	Not specified	Cellular uptake; cytotoxicity; in vivo antitumor efficacy; weight loss; liver toxicity; lymphopenia	FTY720 provides chemosensitization to docetaxel in triple-negative breast cancer. Encapsulation of both drugs in CNPs improves targeting and reduces toxicity.
15	El-Ashmawy, N. E., et al. (2017) .[30]	In vivo study	Female albino mice with solid Ehrlich carcinoma	Treatment with doxorubicin and/or thymoquinone loaded into F2 gel	This study used a novel delivery system for doxorubicin (DOX) and thymoquinone (TQ) by using poly-N-acetyl glucosamine nanofibers, also known as F2 gel. F2 gel alone: 100 µL/mouse Free DOX: 5 mg/Kg dissolved in normal saline TQ: 3 mg/mouse dissolved in polyethylene glycol DOX+F2 gel: 200 µL containing 100 µg of DOX TQ+F2 gel: 200 µL containing 3 mg of TQ DOX+TQ+F2 gel combination: 300 µL containing 100 µg of DOX and 3 mg of TQ	28 days	Tumor volume; cardiac markers (LDH and CK-MB); lipid peroxide in cardiac tissue; anti-apoptotic protein Bcl-2; P53 gene expression in tumor tissue	Thymoquinone enhances the cytotoxic effects of doxorubicin and limits its cardiac toxicity. Loading both drugs into F2 gel shows remarkable anti-cancer activity.
16	Kumar, P., et al. (2018). [32]	In vitro study	MDA-MB-231 and HepG2 cells	Treatment with doxorubicin-loaded PTN; pre-treatment with NAG	Not mentioned	48 hours	Cell viability assay; flow cytometry analysis; confocal microscopy	PAMAM-Trypto phan-(N-acetylglu cosamine) [PTN] is a pH-sensitive nanocarrier for targeted anti-cancer drug delivery via GLUT transporters.
17	Efimova, E. V., et al2019. [33]	In vitro and in vivo study	MCF7 human mammary carcinoma cells; xenograft tumors	Modulation of O-GlcNAcylation; radiation treatment; treatment with GlcNAc	Doxycycline: 1µg/mL PUGNAc (O-(2-Aceta-mido-2-deoxy-D-glucopyranosylidene) amino-N-phenylcarba-mate): 50 µM for cell lysate preparation. 30 mg/kg administered by oral gavage in mice for tumor studies. Alloxan: 50 mg/kg administered by oral gav age in mice for tumor studies. GlcNAc (N-Acetyl-D-glucosamine): 200 mg/kg	ranging from 1 hour for proteomic analysis to 7 days for immunohistochemistry analysis of tumor sections.	Proteomic profiling; DSB repair; cell proliferation; cell senescence	Promoting O-GlcNAcylation protects tumor xenografts against radiation. Suppressing O-GlcNAcylation delays DSB repair , reduces cell proliferation, and increases senescence.
18	Valin ezhad Sani, F., et al (2021). [14]	In vitro study	BCRP-overexpressing breast cancer MCF-7/MX cells	Treatment with glucosamine and mitoxantrone	Glucosamine: Used at concentrations of 0.5 and 1 mM in combination with mitoxantrone	72 hours	MTT assay; flow cytometry analysis of mitoxantrone accumulation; real-time RT-PCR of BCRP and EMT-related markers expression	Glucosamine downregulates BCRP expression and increases mitoxantrone cytotoxicity in breast cancer cells.

Continued Table 2.

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No.	Author, date	Study design	Sample Characteristics [Sample size (n), age, gender	Intervention/ dosage	dose	Duration/ Follow-up	Outcome Measurements	Main outcome
19	Bhura, N., et al. (2022) .[34]	In silico study	Not specified	Molecular docking of basil polysac charides against epigenetic targets (HDAC1-2, 4-8, and HAT)	This study did not involve in vitro or in vivo experiments with specific doses of basil polysaccharides.	Not applicable	Binding affinity	Basil polysaccharides show consistent binding potential against epigenetic targets (HDAC1-2, 4-8, and HAT) involved in breast cancer.
20	Ramezani-Aliakbari, M., et al. (2022). [35]	In vitro study	Breast cancer cell lines	Treatment with POMo@SBA-PDA-Glu NPs; treatment with free POMo	Not mentioned	Not specified	Hydrodynamic size; zeta potential; loading content per cent; pH-responsive release profile; MTT assay; Annexin V-FITC apoptosis detection	POMo@SBA-PDA-Glu NPs show increased anticancer activity against breast cancer cell lines compared to free POMo, with the highest cellular up take and apoptosis in MDA-MB-231 cells.
21	Li, H., et al. (2023). [36]	In vitro study	MDA-MB-231 cells	Treatment with chitosan oligosaccharides, glucosamine, and doxorubicin	-The study tested different concentrations of chitotriose, ranging from 6.25 to 100 µM, in combination with doxorubicin. -The study shows the effects of chitotriose preincubation time on cell viability, with doxorubicin used at a concentration of 4.3 mM. This suggests that 4.3 mM might be the IC50 value determined for doxorubicin in this specific study	varying follow-up durations for different experiments examining the effects of chitotriose on the antitumor activity of doxorubicin in MDA-MB-231 cells. The shortest follow-up time mentioned is 1 hour, used to assess the cellular uptake of doxorubicin using confocal laser scanning microscopy (CLSM). The longest follow-up time noted is 24 hours, used for cell viability assays to determine the effects of chitotriose and doxorubicin, alone and in combination, on cell growth	Antitumor activity; doxorubicin entry into cell nuclei; morphological changes; transcriptional analysis; siRNA test; function assay	Chitotriose enhances the antitumor activ ity of doxorubicin in MDA-MB-231 cells by promoting doxorubicin entry into cell nuclei and upregulating Egr1.
22	Mishra, A., et al. (2024). [38]	In vitro study	Human MCF-7 and MCF-7/TAMR cells	Not specified	D-GlcNAc: Varying concentrations (0.5 mM, 1 mM, 2 mM, and 4 mM) were used to treat MCF-7 and 4T1 cell lines for 72 hours. D-GlcNAc: 2 mM was administered intraperitoneally to mice daily for 28 days. D-GlcNAc was found to decrease cell proliferation and increase apoptosis in breast cancer cells.	The metabolite extraction process involved severa freeze-thaw cycles and centrifugation steps, suggesting a duration of a few hours. The GC-MS analysis, used to separate and identify metabolites, was conducted with a defined temperature program and a total run time of approximately 35 minutes	Metabolite extraction; GC-MS analysis; univariate and multivariate analysis	Tamoxifen-resistant breast cancer cells exhibit dysregulation of various metabolic processes, including valine, leucine, and isoleucine degradation and the Citric Acid Cycle.

4 mM D-GlcNAc significantly reduced cell proliferation in MCF-7 and 4T1 cell lines, while increasing Fas expression and the number of apoptotic cells compared to untreated cultures ($p < 0.01$ - $p < 0.0001$). D-GlcNAc administration also led to a notable decrease in tumor size, mitosis, and angiogenesis in the post-treatment group versus the control group ($p < 0.01$ - $p < 0.0001$). Furthermore, molecular docking and dynamic analysis indicated a strong binding affinity of D-GlcNAc to the HER2 protein, which plays a role in tumor progression and cell signaling. In conclusion, our study highlights the positive effects of D-GlcNAc on breast cancer cells, leading to increased apoptosis and Fas expression. The observed binding affinity to HER2 suggests a potential mechanism of action, supporting D-GlcNAc's role as a potential anti-tumor agent for breast cancer treatment.

Woodman, J. L., et al. (2015) [28] Treatment with doxorubicin (DOX)-loaded PTN led to a significantly higher apoptotic rate (25%) compared to free DOX or DOX-loaded PAMAM (9%). The enhanced cytotoxicity of DOX-loaded PTN was attributed to its pH-responsive drug release, efficient cellular uptake, and improved nuclear localization. The findings suggest that PTN is a promising nanocarrier for targeted cancer therapy.

Alshaker, H., et al. (2017) [29] This study reveals for the first time that FTY sensitizes triple-negative breast cancer (TNBC) cells to docetaxel (DTX), allowing a four-fold reduction in the effective dose. Both drugs were successfully encapsulated in PLGA complex nanoparticles (CNPs) with a size of approximately 100 nm, enabling sequential and sustained release. In TNBC cell lines and mouse models, CNPs demonstrated comparable efficacy to traditional therapies while reducing the effective drug dosage. Moreover, CNPs significantly alleviated chemotherapy side effects, including weight loss, liver toxicity, and lymphopenia. Overall, these findings highlight the potential of FTY and CNPs for enhanced cancer treatment. The encapsulation method improves targeting, minimizes off-target toxicity, and reduces FTY-induced lymphopenia.

El-Ashmawy, N. E., et al. (2017) [30] The incidence of breast cancer is rising globally, prompting the need for new treatment approaches. This study evaluated the effects of doxorubicin (DOX) and thymoquinone (TQ)

nanomatrix on enhancing cytotoxicity and reducing DOX-related cardiotoxicity in solid Ehrlich carcinoma (SEC)-bearing mice. Mice were divided into eight groups, receiving various combinations of DOX and TQ loaded into an F2 gel, a fully-acetylated poly-N-acetyl glucosamine nanofiber. On day 28, the study measured cardiac markers, lipid peroxides, tumor Bcl-2 levels, and P53 gene expression. Results indicated significant reductions in tumor volume, cardiac markers, and tumor Bcl-2 levels with DOX and/or TQ, particularly with the co-treatment of DOX+TQ+F2 gel, which was the most effective. The use of TQ as an adjuvant therapy with DOX improved cytotoxic effects while limiting cardiac toxicity. Overall, the combination therapy exhibited remarkable anti-cancer activity.

Kumar, P., et al. (2018). [32] This research focused on developing a pH-sensitive unimolecular dendritic nanocarrier called PAMAM-Tryptophan-NAG (PTN) for targeted anti-cancer drug delivery via GLUT transporters. The PTN nanocarrier was characterized by techniques such as 1H NMR, DSC, and dynamic light scattering. The hydrodynamic diameter of PTN was found to be 54.3 ± 11.4 nm as measured by DLS. DOX loading in PTN (18.6±0.78 weight %) was significantly ($P<0.001$) higher than in PAMAM (11.2±0.45 weight %). DOX-loaded PTN demonstrated pH-sensitive drug release and significantly higher cytotoxicity ($P < 0.001$) against breast cancer cells than PAMAM. The percentage viability after 48 h in MDA-MB-231 cells was found to be 5.0±2.32% for free DOX, 18.3±2.91% for PAMAM-DOX, and 5.9±0.55% for PTN-DOX.

Efimova, E. V., et al. (2019) [33] conducted the effect of the hexosamine biosynthetic pathway (HBP) and protein O-GlcNAcylation on the DNA damage response in cancer cells. Researchers used a dual reporter system in MCF7 cells to observe the formation and resolution of ionizing radiation-induced foci (IRIF). Silencing OGT with shRNA-miRs led to persistent DNA damage, reduced cell proliferation, and increased senescence in xenograft tumors, as evidenced by increased γH2AX, decreased Ki-67, and increased SA-β-Gal staining, respectively. Conversely, inhibiting OGA with PUGNAc or treating with GlcNAc increased O-GlcNAcylation and protected irradiated tumors, resulting in decreased γH2AX, increased Ki-67, and decreased SA-β-Gal staining. The study found that 16%, 24%, and 10% of shScr, shOGT, and shOGA cells, respectively, retained numerous persistent foci (>60 per cell) 5 days after irradiation. Clonogenic assays showed that shOGT cells had increased radiation sensitivity (surviving fraction at 2 Gy, $SF2 = 0.58 \pm 0.02$) compared to control ($SF2 = 0.89 \pm 0.04$) or shOGA cells ($SF2 = 0.94 \pm 0.04$). These results suggest that targeting O-GlcNAcylation could be a potential strategy for cancer treatment.

Valinezhad Sani, F., et al. (2021) [14] conducted the effect of glucosamine on mitoxantrone (MX) resistance in breast cancer cells. The IC50 values for MCF-7/MX cells exposed to MX in the presence of glucosamine at concentrations of 0, 0.5, and 1 mm for 72 hours were 3.61 ± 0.21, 0.598 ± 0.041, and 0.284 ± 0.016 µm, respectively. Glucosamine significantly reduced the expression of BCRP mRNA in MCF-7/MX cells ($P < 0.01$ and $P < 0.001$ for 0.5 and 1 mm GlcN, respectively). Glucosamine treatment did not significantly affect the intracellular accumulation of MX in resistant breast cancer cells. The mean fold increase in BCRP mRNA expression in MCF-7/MX cells compared to parental MCF-7 cells was approximately 3224.81 ± 513.99. Glucosamine did not have a significant effect on the expression of EMT-related markers in breast cancer cells. The study suggests that glucosamine could be a potential candidate for overcoming multidrug resistance in breast cancer treatment.

Bhura, N., et al. (2022) [34] conducted various sugar derivatives, including glucosamine, glucuronic acid, rhamnose, galactose, mannose, glucose, and xylose, as having consistent binding potential against epigenetic targets (HDAC1-8 and HAT) involved in breast cancer (BC). It is the first report to explore the potential of bioactive polysaccharides (BPSs) against these epigenetic targets. The findings could improve understanding of how BPSs work against these targets in BC. Further experimental validation is needed to confirm BPSs as promising inhibitors for epigenetic regulation in breast cancer.

Ramezani-Aliakbari, M., et al. (2022) [35] The optimized nanoparticles (NPs) had a hydrodynamic size of 195 nm, a zeta potential of -18.9 mV, a 45% loading content, and a pH-responsive release profile. These targeted NPs demonstrated enhanced anticancer activity against breast cancer cell lines, with the highest cellular uptake and apoptosis observed in MDA-MB-231 cells. Compared to free POMo, the NPs were more effective. The study concludes that POMo@SBA-PDA-Glu NPs could be a promising anticancer candidate for future research.

Li, H., et al. (2023) [36] conducted Preincubation with chitotriose enhanced doxorubicin's nuclear entry and induced cell changes. Mechanistically, the early growth response 1 (Egr1) gene was found to regulate its downstream gene Gadd45a, enhancing the suppressive effect on cancer cells. These findings highlight chitotriose's potential in TNBC therapy.

Mishra, A., et al. (2024) [38] Univariate analysis identified 35 elevated and 25 downregulated metabolites in tamoxifen-resistant (TAMR) cells, with N-acetyl-D-glucosamine, lysine, uracil, and others being upregulated, while hydroxyproline, glutamine, and additional metabolites were downregulated. Multivariate analysis showed distinct metabolite profiles between resistant and non-resistant cells. Key affected pathways include the Citric Acid Cycle, Warburg effect, and amino acid degradation. These metabolic disruptions provide insights into the mechanisms of tamoxifen resistance. The findings highlight the role of altered metabolism in understanding tamoxifen resistance in breast cancer therapy.

Discussion

The findings of this systematic review underscore the emerging potential of glucosamine as a therapeutic agent in breast cancer treatment. Glucosamine and its derivatives demonstrate a multifaceted role, influencing tumor biology through mechanisms such as apoptosis

induction, modulation of glycosylation pathways, and anti-inflammatory effects. Notably, the interaction of N-acetyl-D-glucosamine with HER2 receptors and its inhibition of key cancer-related pathways, including NF-κB and transglutaminase 2, suggests a targeted therapeutic mechanism that may complement existing treatments. However, the heterogeneity of study designs and the variability in outcomes highlight the necessity for more robust, large-scale investigations. The possible mechanisms are discussed as follow:

1. Surface Carbohydrate Disruption and Tumor Formation

• Key Findings: Arcaro et al. (2004) [19] demonstrated that disrupting surface carbohydrates with enzymes like beta-galactosidase inhibited foci formation in MCF-7 breast cancer cells. This suggests surface carbohydrates play a significant role in tumor development.

• Implications: Targeting cell surface carbohydrates could be a promising therapeutic approach to inhibit tumor growth without damaging healthy cells.

2. Glucosamine's Role in Cancer Stem Cells (CSCs)

• Key Findings: Hosea et al. (2018) [31] found that glucosamine reduced the expression of stemness genes in breast CSCs, indicating decreased tumorigenicity. Similarly, Baysal et al. (2024)(37) showed that glucosamine derivatives, such as D-GlcNAc, promoted apoptosis and increased Fas expression in breast cancer cells.

• Implications: Glucosamine and its analogs could be effective in targeting cancer stem cells, potentially reducing the ability of tumors to self-renew and spread.

3. Imaging and Tumor Response Assessment

• Key Findings: Yang et al. (2004) [20] used the radiolabeled glucosamine analog 99mTc-EC-DG for tumor imaging, successfully visualizing tumors in mice and assessing therapy response. Xiong et al. (2007) (22) highlighted the selective tumor-targeting ability of 188Re-DTPA-DG, another glucosamine derivative, which induced significant apoptosis in breast cancer cells.

• Implications: Glucosamine analogs offer valuable tools for non-invasive tumor imaging and monitoring treatment efficacy in real-time, which can enhance personalized cancer therapy.

4. O-GlcNAcylation and Drug Resistance

• Key Findings: Kanwal et al. (2013)(26)observed that increased O-GlcNAcylation levels protected MCF-7 breast cancer cells from tamoxifen-induced cell death by downregulating estrogen receptor α (ERα) expression. This effect contributed to tamoxifen resistance.

• Implications: Glucosamine's involvement in the O-GlcNAcylation pathway suggests that it might influence drug resistance in hormone receptor-positive breast cancers, indicating a potential target to overcome resistance to therapies like tamoxifen.

5. Glucosamine's Role in Multidrug Resistance

• Key Findings: Valinezhad Sani et al. (2021)(14) found that glucosamine reduced the expression of BCRP mRNA in multidrug-resistant breast cancer cells, potentially enhancing the efficacy of chemotherapeutic agents.

• Implications: Glucosamine may help mitigate drug resistance in cancer treatment, offering a new strategy to improve chemotherapy outcomes.

6. Epigenetic and Combination Therapy Potential

• Key Findings: Bhura et al. (2022)(34) identified sugar derivatives, including glucosamine, as promising inhibitors of epigenetic targets linked to breast cancer. These derivatives could improve treatment efficacy when combined with existing therapies.

• Implications: Combining glucosamine with conventional therapies may enhance drug delivery, targeting cancer cells more effectively while reducing side effects.

Limitations

This study is limited by its reliance on available literature, which may introduce publication bias, as studies with negative findings are less likely to be published. The variability in study designs and methodologies among the included studies hindered a comprehensive meta-analysis, limiting the ability to draw definitive conclusions. Additionally, the analysis predominantly focused on glucosamine, without considering other dietary factors or supplements that might influence breast cancer risk. Lastly, the studies examined did not uniformly control for confounding variables such as genetics, lifestyle factors, and comorbidities, which could impact the findings.

Future Study

Future research should aim for large-scale, well-designed longitudinal studies to clarify the relationship between glucosamine intake and breast cancer risk. Investigating the underlying mechanisms through which glucosamine exerts its effects, particularly its interaction with cellular signaling pathways and the gut microbiome, will be crucial. Moreover, exploring potential differences in responses based on demographics such as age, sex, and genetic predispositions can provide deeper insights. It would also be beneficial to include comparative studies of glucosamine against other dietary supplements to understand its unique contributions to cancer prevention and treatment.

In conclusion, this comprehensive review highlights the complex relationship between glucosamine intake and breast cancer risk, suggesting potential protective effects through various biological mechanisms, including anti-inflammatory properties, modulation of cellular signaling pathways, and influence on glycosylation. While several studies indicate that glucosamine may inhibit breast cancer growth and reduce mortality rates associated with certain cancers, the variability in study designs and outcomes emphasizes the need for further investigation. Future research should focus on large-scale longitudinal studies to validate these findings and explore how demographic factors influence the efficacy of glucosamine. Understanding the underlying mechanisms and interactions with other dietary components will be essential in establishing glucosamine's role in cancer prevention and treatment, paving the way for targeted therapeutic strategies.

Author Contribution Statement

All authors contributed equally in this study.

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