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# THE IMPACT OF AGE-RAGE PATHWAY IN BREAST CANCER: NOVEL STRATEGIES FOR TREATMENT AND PREVENTION

Jyotsana Rashmi

HIMT College of Pharmacy, Knowledge Park-1, Greater Noida, Gautam Buddha Nagar - 201310, Uttar Pradesh, India.

**Keywords:**

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**Correspondence to Author:**
**Jyotsana Rashmi**

Research Scholar,
HIMT College of Pharmacy,
Knowledge Park-1, Greater Noida,
Gautam Buddha Nagar - 201310,
Uttar Pradesh, India.

**E-mail:** jyotsanarashmi05@gmail.com

**ABSTRACT:** The receptor for advanced glycation end-products (RAGE) and its ligands, particularly advanced glycation end-products (AGEs), serve as a crucial molecular link between diabetes and breast cancer. Chronic hyperglycemia and insulin resistance in diabetes promote excessive AGE formation, which, upon binding to RAGE, triggers inflammatory and oncogenic signaling cascades, including NF-κB, PI3K/Akt, MAPK, and JAK/STAT pathways. These pathways drive oxidative stress, chronic inflammation, and epithelial-to-mesenchymal transition (EMT), fostering a tumor-promoting microenvironment. In breast cancer, sustained RAGE activation enhances cancer cell proliferation, invasion, angiogenesis, and immune evasion while also contributing to therapy resistance. Additionally, metabolic reprogramming associated with diabetes, such as the Warburg effect and increased insulin/IGF-1 signaling, synergizes with RAGE-mediated tumor progression. The persistent activation of the AGE-RAGE axis creates a self-sustaining loop of inflammation and oxidative stress, exacerbating both metabolic dysfunction and tumorigenesis. Understanding the intricate crosstalk between diabetes and breast cancer through this axis highlights the potential of targeting RAGE as a novel therapeutic strategy for managing both conditions. This review explores the molecular mechanisms underpinning the AGE-RAGE axis in diabetes and breast cancer, emphasizing its role in disease progression and potential clinical implications.

**INTRODUCTION:** Cancer often referred as a group of diseases that are distinguished by the uncontrolled proliferation of cells and the dissemination of the disease to adjacent tissues, frequently resulting in the formation of tumors [1]. According to a WHO estimate, cancer is a primary cause of mortality globally, accounting for around 10 million deaths in 2020, or about one in six deaths globally [2].

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The estimated number of incident cases of cancer in India for the year 2022 was found to be 14,61,427(100 cases per 100,000) [3]. In India, one in nine people are likely to develop cancer in his/her lifetime. The global cancer burden is expected to be 28.4 million cases by 2040 [4]. Smoking, diet, and exposure to carcinogens are among the lifestyle choices that contribute to its development, as well as genetic mutations and environmental factors.

Lung, breast, prostate, and colorectal cancer are among the most prevalent forms [5]. Fatigue, persistent pain, tumors, and unexplained weight loss are among the symptoms that may be present. As a result of altered energy production and nutrient utilization in cells, cancer is becoming more widely recognized as a metabolic disease [6].

In contrast to healthy cells, which predominantly rely on oxidative phosphorylation, cancer cells frequently transition to glycolysis, a phenomenon known as the Warburg effect, even in oxygen-rich conditions [7]. This metabolic reprogramming facilitates rapid proliferation, resistance to therapy, and the evasion of apoptosis. Dysregulated lipid and amino acid metabolism further fuel tumor growth and immune evasion [6]. Globally, breast cancer is most rising concern of mortality for women and the second most prevalent death cause [8]. According to the World Health Organization (WHO), there were 2.3 million new cases of breast cancer found globally and approximately 685,000 deaths found globally in 2020. As of the end of 2020 breast cancer found 12.5% of all new annual cancer cases worldwide and there were 7.8 million women alive who were diagnosed with breast cancer in the past 5 years, making it the world's most prevalent [9].

According to the American Cancer Society, more than 3.5 million women are currently living with breast cancer or have been treated for it. In 2020, there were an estimated 3,886,830 women living with female breast cancer in the United States. Numerous morphological, molecular, and biochemical characteristics that affect the course of the illness, prognosis, and responsiveness to treatment define this heterogeneous malignancy. Approximately 80% of breast cancer cases are invasive, which means that a tumor may move from the breast to other parts of the body. Breast cancer mainly affects women aged 50 and older, however it may also afflict women under the age of 50. Men may also acquire breast cancer [10, 11].

In 2022, 2.3 million women were diagnosed with breast cancer, and 670,000 died worldwide. It affects women of all ages after puberty, although the incidence rises later in life. Breast cancer and their typer are categorized according to their hormone dependence; for example, they are called ER-positive or ER-negative [12]. Particularly, ERα-positive breast cancer accounts for over 70% of situations. Based on their immunohistochemistry (IHC) features (hormone status), breast cancer can be divided clinically into three primary kinds. These are triple negative, HER2 positive (HER2+), and hormone receptor positive [13]. Breast cancers that have Estrogen receptor-positive (ER+) or progesterone receptor-positive (PR+) characteristics are known as hormone receptor-positive breast cancers. Hormone receptor-positive breast cancer account for around 85% of all cases. Luminal A and Luminal B are the two variants of hormone receptor-positive breast cancer [14]. Luminal A cancers are often HER2-negative (HER2-) and ER+ or PR+. Luminal B cancers are often HER2+ (or HER2- with elevated Ki67) and ER+ and/or PR+ [15]. Despite of that, Diabetes mellitus (DM) is a concerning significant public health issue, and it is the 10 top most cause of mortality in the United States, Europe, and industrialized nations. Diabetes mellitus (DM) is a metabolic disease, involving inappropriately elevated blood glucose levels [16]. DM has several categories, including type 1, type 2, maturity-onset diabetes of the young (MODY), gestational diabetes, neonatal diabetes. Its incidence and prevalence are increasing day by day [17].

According to the national diabetes statistics report 38.4 million people of all ages or 11.6% of the U.S. population had diabetes. 38.1 million adults aged population has been diagnosed (18 years) diabetes [18]. Global prevalence of type 2 diabetes is projected to increase to 7079 individuals per 100,000 by 2030, reflecting a continued rise across all regions of the world [19]. The main subtypes of DM are Type 1 diabetes mellitus (T1DM) and Type 2 diabetes mellitus (T2DM), which classically result from defective insulin secretion (T1DM) and/or action (T2DM). T1DM presents in children or adolescents, while T2DM is thought to affect middle-aged and older adults who have prolonged hyperglycemia due to poor lifestyle and dietary choices.

The pathogenesis for T1DM and T2DM is drastically different, and therefore each type has various etiologies, presentations, and treatments. Hyperglycemia, primarily caused by untreated insulin resistance, is a dominant factor of type 2 diabetes [20]. Chronic hyperglycemia in case of insulin resistance leads to production of advance glycation end product (AGE), a family of compounds of diverse chemical nature that are the products of nonenzymatic reactions between reducing sugars and proteins, lipids, or nucleic acids [21]. The glycation triggered by hyperglycemia is a comprehensive process, and it has major

structural and functional ramifications. Cancer often has a higher metabolism linked to higher glycolytic rates, that also stimulate the production of AGEs [22, 23]. As AGEs can accelerate the advancement and spread of breast cancer, researches have recently revealed the direct effects of diabetes-related hyperglycemia and hyper-insulinemia and breast cancer relation [24]. In case of Diabetes chronic hyperglycemia is the indicator of unhealthy glycemic management. The brain and other glucose-dependent tissues require a constant, uninterrupted supply of glucose, which is maintained by the pancreas actions in preventing both postprandially and interprandial hypoglycemia. The evolution and expansion of diabetic complications, such as cardiovascular disease, kidney disease, retinopathy, and neuropathy, can be significantly impacted by even brief episodes of hyperglycemia or hypoglycemia or by increased glycemic variability around healthy mean glucose levels [25]. It is currently known that AGEs, as ligands, activate many intracellular signaling cascades, resulting in a variety of pathological consequences after binding to AGE receptors (RAGE) [26]. Several downstream effectors of the RAGE pathway have been linked to cancer immunity, cell proliferation, angiogenesis, and metastases. Targeted RAGE silencing has been shown to limit breast cancer cell growth and invasion. Thus, it is fair to infer that AGEs generated by diabetics may enhance breast cancer invasion and metastasis via RAGE-mediated signaling pathways.

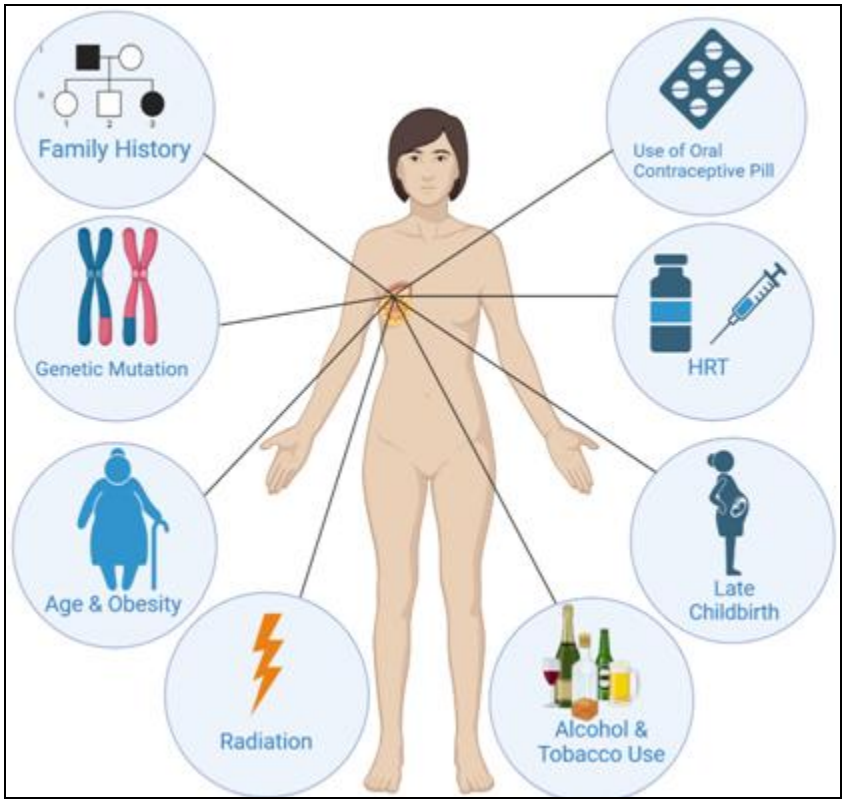


**FIG. 1: REPRESENT CAUSES AND RISK FACTOR ASSOCIATED WITH BREAST CANCER**

**RAGE Structure, Expression, Function:** The Receptor for Advanced Glycation End Products (RAGE) is a multi-ligand receptor of the immunoglobulin (Ig) superfamily, structurally divided into three segments: extracellular, transmembrane, and intracellular [27]. The extracellular segment, responsible for ligand binding, comprises three Ig domains: V-type, C1-type, and C2-type. This is followed by the transmembrane segment and a short, highly charged intracellular segment that plays a key role in signal transduction [28, 29]. The human RAGE gene is located on the major histocompatibility complex locus in the class III region of chromosome 6p21.3, a gene-dense region containing many inflammatory genes [30]. In addition to cell surface RAGE, two soluble forms of RAGE exist: sRAGE and esRAGE. sRAGE is generated by proteolytic

cleavage of full-length RAGE (flRAGE) by matrix metalloproteinases (MMPs), integrin α (ITGα), and ADAM-10 [31]. In contrast, esRAGE is an endogenously secreted splice variant. Both forms bind RAGE ligands, preventing their interaction with flRAGE, thereby functioning as ligand inhibitors in humans. Cell surface RAGE and its ligand interactions trigger inflammatory signaling cascades both *in-vitro* and *in-vivo*, contributing to the pathophysiology of various diseases [32]. Recent studies suggest that nuclear RAGE plays a distinct role in DNA damage repair, though its exact mechanism and involved cell types remain unclear [33]. Thus, RAGE exhibits a dual function: as a cell surface receptor, it drives pro-inflammatory responses, while in the nucleus, it participates in DNA repair.

**Rage Ligands:** Because of the presence of multiple domains (V, C1, and C2), receptor isoforms, and polymorphisms, RAGE is able to interact with a series of different ligands.

**AGEs:** Advanced Glycation End Products (AGEs) are a diverse group of compounds formed through the non-enzymatic glycation of proteins, lipids, and nucleic acids by reducing sugars via the Maillard reaction, which progresses through three stages: early glycation, advanced glycation, and AGE formation. Initially, reducing sugars react with free amino groups of proteins, forming Schiff bases, which undergo further rearrangement to produce Amadori products [34, 35]. Over time, these intermediate products undergo oxidation, dehydration, and condensation, leading to the formation of irreversible AGEs. AGEs can be classified into fluorescent AGEs (such as pentosidine), non-fluorescent AGEs (such as Nε-carboxymethyl-lysine [CML] and Nε-carboxyethyl-lysine [CEL]), and cross-linking AGEs (such as glucosepane) [36, 37]. The formation of AGEs is accelerated under hyperglycemic conditions, oxidative stress, and inflammation, making them critical in the pathology of diabetes, neurodegenerative diseases, and cardiovascular disorders [38]. AGEs exert their effects by modifying structural proteins, impairing their function, and through interaction with the Receptor for Advanced Glycation End Products (RAGE), triggering intracellular signaling cascades that promote inflammation, oxidative stress, and fibrosis [39, 40].

Additionally, AGEs can be derived endogenously through metabolic reactions or exogenously through diet, particularly in heat-processed foods [41]. The accumulation of AGEs contributes to tissue damage, vascular dysfunction, and accelerated aging, making their regulation an important therapeutic target in metabolic and age-related diseases [42].

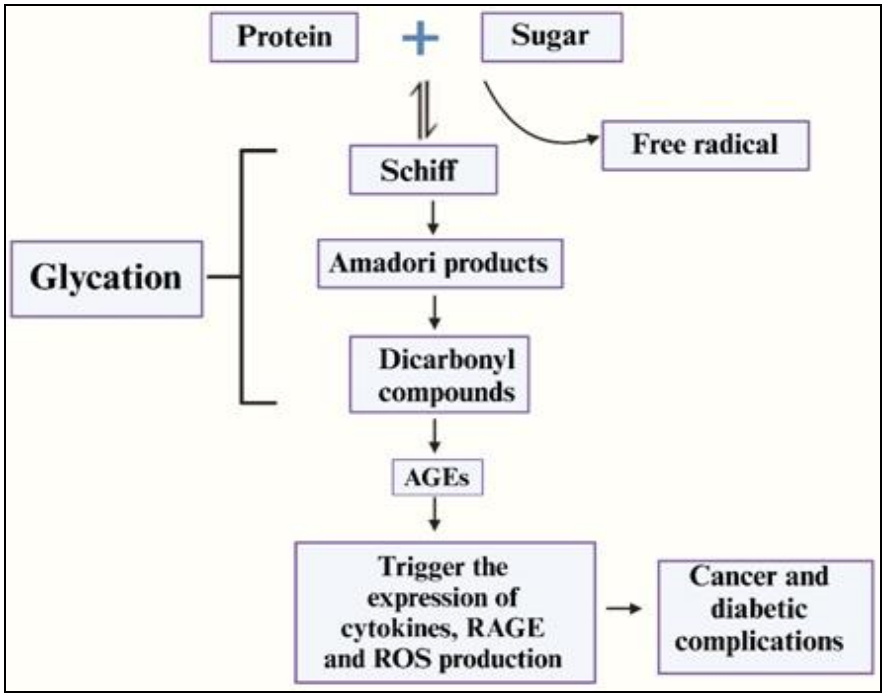


**FIG. 2: REPRESENT FORMATION OF AGE**

**HMGB1:** High Mobility Group Box 1 (HMGB1) is a highly conserved chromatin-binding protein that functions as a nuclear, cytoplasmic, and extracellular signalling molecule, playing crucial roles in DNA organization, transcriptional regulation, and immune responses [43, 44]. Structurally, HMGB1 consists of two DNA-binding domains (Box A and Box B) and an acidic C-terminal tail, which regulate its interactions with DNA and proteins. HMGB1 exists in different forms based on its redox state, including fully reduced HMGB1, disulfide HMGB1, and oxidized HMGB1, each exhibiting distinct biological activities [45].

In its fully reduced form, HMGB1 primarily acts as a chemotactic factor by binding to CXCL12 and interacting with CXC chemokine receptor 4 (CXCR4), promoting cell migration and tissue repair. Disulfide HMGB1, characterized by an intramolecular disulfide bond in Box B, functions as a pro-inflammatory mediator by activating Toll-like receptor 4 (TLR4) and RAGE, leading to NF-κB activation and cytokine release. Oxidized HMGB1, which contains terminally oxidized cysteines, loses its cytokine and chemotactic activities and is involved in immunosuppression and resolution of inflammation [46, 47]. HMGB1 is passively released from necrotic and damaged cells or actively secreted by immune cells like macrophages, dendritic cells, and neutrophils under inflammatory conditions. Its extracellular release is triggered by cellular stress, infection, hypoxia, and oxidative damage, where it serves as a damage-associated molecular pattern (DAMP) molecule, amplifying immune responses. HMGB1-mediated signalling is involved in sepsis, cancer, neuroinflammation, and autoimmune diseases, making it a potential therapeutic target for inflammatory and immune-related disorders [48, 49].

**S100 Protein:** S100 proteins are a large family of calcium-binding proteins belonging to the EF-hand super family, involved in diverse cellular functions, including calcium signalling, inflammation, immune response, cell proliferation, and apoptosis [50, 51]. The S100 family consists of more than 20 members (e.g., S100A1, S100A4, S100B, S100P, S100A12) that exhibit tissue-specific expression and function both intracellularly and extracellularly [51]. Intracellularly, S100 proteins act as calcium sensors and signal transducers, modulating various targets such as enzymes, cytoskeletal proteins, and transcription factors. Extracellularly, S100 proteins function as damage-associated molecular patterns (DAMPs) by binding to Receptor for Advanced Glycation End Products (RAGE) and Toll-like receptors (TLRs), initiating inflammatory and immune responses [52]. Structurally, S100 proteins typically form homodimers, heterodimers, or oligomers, which influence their biological activity and target interactions. Their formation is tightly regulated by calcium, zinc, and redox status, allowing them to mediate signal transduction in response to cellular stress, injury, or infection [53, 54].

Dysregulated S100 expression is implicated in chronic inflammation, neurodegenerative diseases (e.g., Alzheimer's, Parkinson's), cancer progression, and cardiovascular disorders, where they act as biomarkers and potential therapeutic targets. Elevated levels of S100B are associated with brain injury and neuroinflammation, while S100A4 and S100A12 play key roles in cancer metastasis and atherosclerosis, respectively. Given their broad functional scope, S100 proteins are crucial regulators of cellular homeostasis and pathological processes, making them significant in disease diagnostics and treatment strategies [55, 56].

**Rage in Diabetes:** Because hyperglycaemia in diabetes raises the formation of AGEs, the kidney and other kidney cells such as the glomerular basement membrane, mesangial cells, podocytes, tubular cells, and vascular endothelial cells are overloaded with AGEs, which promotes cellular damage [57, 58]. A guanidine derivative called aminoguanidine inhibits the production of AGE by trapping reactive dicarbon. RAGE is a multi-ligand pattern recognition receptor that plays a pivotal role in diabetes and its complications [59]. Type 2 diabetes mellitus (T2DM) is closely linked to increased RAGE expression through chronic hyperglycaemia, oxidative stress, and inflammation. In T2DM, prolonged hyperglycaemia leads to excessive formation of advanced glycation end-products (AGEs), which serve as primary ligands for RAGE[60,61]. In hyperglycaemic conditions, elevated levels of advanced glycation end-products (AGEs) bind to RAGE, triggering receptor activation and downstream signaling cascades.

This activation primarily involves the NF-κB pathway, where AGEs-RAGE interaction leads to the activation of NADPH oxidase, increasing reactive oxygen species (ROS) production. ROS, in turn, activates NF-κB, which translocate to the nucleus and promotes the transcription of pro-inflammatory cytokines (TNF-α, IL-6), adhesion molecules (VCAM-1, ICAM-1), and further RAGE expression, creating a positive feedback loop [62–64]. Additionally, the RAGE signaling pathway interacts with the MAPK and JAK/STAT pathways, contributing to inflammation, apoptosis, and vascular dysfunction. In type 3 diabetes, or Alzheimer disease-related diabetes, RAGE also mediates amyloid-β-induced neuroinflammation and oxidative stress, exacerbating neuronal damage. The persistent activation of RAGE signaling in diabetes leads to chronic inflammation, endothelial dysfunction, and progression of diabetic complications such as nephropathy, retinopathy, and atherosclerosis [65, 66]. Insulin resistance plays a crucial role in accelerating the formation of AGEs, which further contribute to metabolic dysfunction and diabetic complications. In insulin-resistant states, such as type 2 diabetes mellitus (T2DM) and obesity, impaired insulin signaling leads to chronic hyperglycemia. Persistent high blood glucose levels enhance the non-enzymatic glycation of proteins, lipids, and nucleic acids, forming Schiff bases and Amadori products, which ultimately undergo irreversible chemical modifications to generate AGEs [67, 68]. Additionally, insulin resistance is associated with increased oxidative stress due to mitochondrial dysfunction and excessive production of reactive oxygen species (ROS). Oxidative stress promotes AGE formation by accelerating glycoxidation reactions and lipid peroxidation-derived AGE precursors, such as malondialdehyde (MDA) and 4-hydroxy-2-nonenal (HNE) [69].

Moreover, insulin resistance impairs the clearance of AGEs by reducing the expression of AGE-detoxifying enzymes, such as glyoxalase-1, and decreasing the activity of AGE-receptors involved in AGE degradation, such as AGER1. The accumulation of AGEs leads to their interaction with the receptor for advanced glycation end-products (RAGE), activating pro-inflammatory and pro-fibrotic signalling pathways [70, 71].

**TABLE 1: REPRESENT THE VARIOUS LIGAND OF RAGE, THEIR BINDING SITE AND THEIR FUNCTION**

| Ligand | Binding site | Function |
|---|---|---|
| Advanced Glycation End Products (AGEs) | V-type domain | Promotes inflammation, oxidative stress, and diabetic complications |
| HMGB1 | V-type domain | Mediates inflammation, immune response, and cell migration |
| Amyloid-β (Aβ) | V-type domain | Involved in Alzheimer's disease pathology |
| S100 Proteins (S100B, S100A4, S100A12, etc.) | V-type and C1 domains | Regulate inflammation, calcium homeostasis, and tumour progression |
| Protein Diaphanous Homolog 1 (DIAPH1) | Cytoplasmic domain | Facilitates RAGE-mediated intracellular signalling |
| Brain-Derived Neurotrophic Factor (BDNF) | V-type domain | Modulates neuronal survival and synaptic plasticity |
| Epidermal Growth Factor Receptor (EGFR) | V-type and C1 domains | Promotes tumour growth and cell proliferation |
| Myeloid Differentiation Primary Response 88 (MyD88) | Cytoplasmic domain | Links RAGE to TLR-mediated inflammatory responses |
| Transforming Protein Ras Homolog Family Member A (RhoA) | Cytoplasmic domain | Regulates cytoskeletal dynamics and cell migration |
| Toll-Like Receptor 9 (TLR9) | Cytoplasmic domain | Enhances immune activation and inflammation |
| Formyl Peptide Receptors (FPRs) | V-type domain | Modulates immune cell migration and response |
| Leukotriene B4 Receptor 1 (BLT1) | V-type domain | Involved in inflammatory and immune responses |
| Non-Catalytic Region of Tyrosine Kinase Adaptor Protein 1 (NCK1) | Predicted intracellular binding | Regulates intracellular signalling pathways |
| Chromosome 3 Open Reading Frame 52 (C3orf52) | Predicted intracellular binding | Potential role in immune signalling |
| Mitogen-Activated Protein Kinase 5 (MAPK5) | Cytoplasmic domain | Involved in signal transduction and cell survival |

**Rage in Breast Cancer:** Several studies have demonstrated that chronic inflammation plays a significant role in the development of tumours. The activation of many transcription factors, primarily

NF-κB, which controls the production of tumour-promoting cytokines as well as survival genes like Bcl-XL, is crucial for the creation of an inflammatory, pro-tumorigenic milieu [72]. In a positive feed-forward fashion, these soluble substances subsequently attract and activate immune cells of myeloid and lymphoid origin and set off signalling pathways that result in the creation of several pro-inflammatory mediators [73].It has been linked to the development of several malignancies and offers a crucial connection between the build-up of AGEs and cancer through its capacity to activate NF-κB, RAGE signalling, and up-regulation. The presence of AGEs in human cancers was initially demonstrated by immunohistochemical labelling in squamous cell carcinomas of the throat, breast, colon, and leiomyosarcomas, with significant heterogeneity among tumour types [74].

RAGE expression in a panel of breast cancer cell lines was overanalysed. Metastatic TNBC cell lines showed increased RAGE expression, while weakly metastatic ERα+ breast cancer cell lines (MCF7, T47D, and BT474) showed little to no RAGE expression. Research study shows that, RAGE is mostly expressed in breast cancer cell lines that are ERα- and highly metastatic [75, 76]. Assessment of open access Gene Expression Omnibus (GEO) datasets for RAGE expression to assess the relationship between RAGE and ERα-status. According to research on subtype-specific breast cancer, RAGE expression is considerably higher in tumour samples from patients with invasive breast cancer and basal type (mostly TNBC) breast cancer than in non-basal type (mostly ERα+ cancer) and normal breast cancer [77], respectively.

The existence of an inflammatory micro-environment in solid tumours, particularly breast cancers, is now well acknowledged. A member of the immunoglobulin superfamily of cell surface molecules, receptor for advanced glycation end products (RAGE) has been linked to chronic inflammation, which accelerates the development of certain types of cancer [78]. Several molecular signalling pathways, including PI3K/AKT, JAK/STAT, NF-ķB, Ras/MAPK, Rac1/cdc42, p44/p42, p38, and SAP/JNK MAPK, as well as transcription factors, including NF-ķB, STAT3, HIF-1α, AP-1, and CREB, are activated when RAGE is stimulated by its ligands, AGEs, HMGB1, and the S100 group of proteins. By interacting with AGEs, HMGB1, or the S100 group of proteins-which are mostly expressed during pathological circumstances of glycation and inflammation-RAGE functions as a master regulator of the genesis, invasion, and metastasis of tumours [79, 80]. Regardless of the cancer's genesis place, genetic subtype, or stage of development, the receptor-ligand combination is the primary target for both prevention and effective therapy. It gives medications that target RAGE and its ligands preferential cytotoxicity; once these treatments are found, they may be employed in conjunction with traditional chemotherapy to effectively inhibit the growth and spread of malignancies while having no negative effects on healthy cells [79].

**Rage Mediated Signalling Pathway in Breast Cancer:**

**NF – kB signalling Pathway:** One important transcription factor that connects inflammation and cancer is NF-κB. It is crucial for controlling inflammation, cell line survival, and proliferation. AGEs, HMGB1, and S100 proteins bind to RAGE, leading to receptor oligomerization and activation of intracellular adaptor proteins such as Toll/interleukin-1 receptor (TIR) domain-containing adaptor protein (TIRAP) and MyD88.The RAGE signalling pathway activates NADPH oxidase, leading to the generation of reactive oxygen species (ROS), which serve as secondary messengers [81–83].

ROS activates transforming growth factor-beta-activated kinase 1 (TAK1), which subsequently phosphorylates the IκB kinase (IKK) complex. The IKK complex consists of IKKα, IKKβ, and IKKγ (NEMO). Upon activation, IKKβ phosphorylates inhibitor of NF-κB (IκBα), marking it for ubiquitination and subsequent degradation by the proteasome. The degradation of IκBα releases p50/p65 (RelA) heterodimers, allowing them to translocate into the nucleus.Once in the nucleus, NF-κB regulates the expression of multiple genes (TNF-α, IL-6, IL-8, & CCL-2) that contribute to breast cancer progression. NF-κB activation via RAGE promotes tumour invasion and metastasis by increasing the expression of matrix metalloproteinases (MMP-2, MMP-9), which degrade the extracellular matrix (ECM) [84–87].

**MAPK/ERK Pathway:** Many pathophysiological alterations brought on by AGE have been linked to the MAPK pathway. The MAPK/ERK signalling pathway plays a crucial role in breast cancer progression when activated *via* the RAGE [88]. Upon binding of AGEs or other RAGE ligands (such as S100 proteins or HMGB1), RAGE undergoes conformational changes, leading to the recruitment and activation of intracellular adaptor proteins like Src, TGF-β-activated kinase 1 (TAK1), and growth factor receptor-bound protein 2 (GRB2). These adaptors facilitate the activation of Ras, a small GTPase that initiates the classical MAPK/ERK cascade [89, 90]. Activated Ras phosphorylates and activates RAF (Rapidly Accelerated Fibrosarcoma), which subsequently phosphorylates MEK1/2 (MAPK/ERK kinase). MEK1/2 then phosphorylates ERK1/2 (extracellular signal-regulated kinases), leading to their translocation into the nucleus, where they regulate transcription factors such as c-Myc, Elk-1, and AP-1 [91, 92]. These transcription factors drive the expression of genes associated with proliferation (cyclin D1, c-Myc), survival (Bcl-2, Mcl-1), epithelial-to-mesenchymal transition (EMT) markers (Snail, Twist, Zeb1), and invasion (MMP-2, MMP-9) [92]. Additionally, RAGE-mediated ERK activation enhances resistance to apoptosis by modulating Bcl-2 family proteins and upregulating surviving. Chronic activation of the RAGE-MAPK/ERK pathway also fosters a pro-inflammatory tumour micro-environment by inducing cytokine secretion (IL-6, TNF-α) and increasing oxidative stress through NADPH oxidase activation, further sustaining tumour progression. In breast cancer, particularly in aggressive subtypes like triple-negative breast cancer (TNBC), persistent RAGE-ERK signalling promotes tumour cell proliferation, metastasis, and chemoresistance, making it a potential therapeutic target for anti-cancer interventions [93–95].

**JAK/STAT Pathway:** The JAK/STAT (Janus kinase/signal transducer and activator of transcription) signalling pathway plays a crucial role in breast cancer progression when activated via the receptor for advanced glycation end-products (RAGE) [96, 97]. Upon binding of advanced glycation end-products (AGEs) or other RAGE ligands (S100 proteins, HMGB1), RAGE undergoes activation, leading to intracellular signalling cascades, including the recruitment of Janus kinases (JAKs) [98]. Activated JAKs phosphorylate specific tyrosine residues on RAGE-associated adaptor proteins, which in turn serve as docking sites for STAT proteins (primarily STAT3 and STAT5 in breast cancer). These STAT proteins are then phosphorylated, leading to their dimerization and translocation into the nucleus, where they function as transcription factors to regulate genes involved in inflammation, proliferation, invasion, and metastasis [98–100]. The RAGE-induced JAK/STAT activation enhances the expression of key oncogenes and pro-tumorigenic cytokines, such as IL-6, IL-8, and VEGF, contributing to a chronic inflammatory tumour microenvironment. Moreover, sustained STAT3 activation promotes epithelial-to-mesenchymal transition (EMT), increases cancer stem cell-like properties, and induces chemoresistance, all of which contribute to breast cancer aggressiveness [101, 102]. STAT5 activation, on the other hand, has been linked to hormone receptor signalling and tumour growth, particularly in estrogen receptor-positive (ER+) breast cancer subtypes [103]. Additionally, RAGE-mediated JAK/STAT signalling interacts with other oncogenic pathways, including NF-κB and MAPK, amplifying the inflammatory and proliferative signals within the tumour microenvironment. Targeting the JAK/STAT pathway in RAGE-activated breast cancer may provide a promising therapeutic approach to mitigate inflammation-driven tumour progression and improve treatment outcomes [104].

**PI3K/AKT Pathway:** A class of lipid kinases known as phosphoinositide 3-kinase (PI3K) phosphorylates the 3′-OH group of phosphatidylinositol (PI) at intracellular membranes and plasma. The PI3K/Akt signalling pathway plays a crucial role in breast cancer progression when activated via the receptor for advanced glycation end-products (RAGE). Upon binding of AGEs or other RAGE ligands, such as S100 proteins and HMGB1, RAGE undergoes activation, triggering downstream signalling cascades, including the phosphoinositide 3-kinase (PI3K)/Akt pathway [105–107]. Activation of RAGE recruit's adaptor molecules such as Grb2 and SOS, which facilitate PI3K activation by phosphorylating its regulatory subunit (p85) and activating the catalytic subunit (p110) [108]. This leads to the conversion of PIP2 to PIP3, which acts as a

docking site for Akt and phosphoinositide-dependent kinase 1 (PDK1). PDK1 phosphorylates Akt at Thr308, followed by additional phosphorylation at Ser473 by mTORC2, leading to full activation of Akt. Activated Akt promotes breast cancer cell survival, proliferation, and invasion by inhibiting pro-apoptotic factors such as BAD and caspase-9 while upregulating cell cycle regulators like cyclin D1. Additionally, Akt activation suppresses the tumour suppressor PTEN, further amplifying PI3K signalling [109, 110]. RAGE-induced Akt activation also enhances epithelial-to-mesenchymal transition (EMT) by increasing Snail, Twist, and β-catenin levels, facilitating metastasis. Furthermore, Akt activation stimulates mTORC1, promoting protein synthesis, metabolic reprogramming, and angiogenesis, which sustain tumour growth [111].

Chronic RAGE activation in insulin-resistant and inflammatory conditions exacerbates PI3K/Akt-driven breast cancer progression, making it a potential target for therapeutic intervention. In breast cancer, the PI3K/AKT/mTOR pathway is often dysregulated by several pathways, resulting in mutations in tumour suppressor genes such as INPP4B and PTEN phosphatases, as well as increased PI3K activity and/or loss of PI3K inhibitory activities [112, 113]. One of the most often mutated PI3K genes is PIK3CA, which has mutations at two hotspot regions: a histidine residue (H1047) in the kinase domain and an acidic cluster (E542, E545, and Q546) in the helical domain. Activating mutations in the catalytic subunit of p110α directly enhance lipid kinase activity by allowing allosteric movements necessary for catalysis on membranes, whereas mutations on the helical domain mostly rely on the loss of p85-dependent inhibitory action [114, 115].

**RAGE-Dependent Crosstalk with ROS Signalling:** ROS signalling plays a critical role in sustaining chronic inflammation, oxidative stress, and cellular dysfunction in various pathological conditions, including diabetes, neurodegenerative disorders, and cancer [116, 117]. The binding of RAGE ligands, such as AGEs, S100 proteins, and HMGB1, triggers a primary source of ROS production in cells. This activation occurs through the recruitment of intracellular adaptor proteins such as TIRAP and MyD88, which lead to downstream activation of signalling cascades, including NF-κB, MAPK, and PI3K/Akt pathways [118, 119]. The stimulation of NOX increases superoxide ($O_2^-$) production, which undergoes dismutation to hydrogen peroxide ($H_2O_2$), further amplifying oxidative stress. Simultaneously, RAGE activation inhibits antioxidant defines mechanisms by down regulating the expression of key detoxifying enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx) [120, 121]. The excessive accumulation of ROS activates NF-κB, which translocate to the nucleus and upregulates pro-inflammatory cytokines (TNF-α, IL-6, IL-1β), adhesion molecules (VCAM-1, ICAM-1), and matrix metalloproteinases (MMPs), thereby perpetuating a pro-inflammatory microenvironment.

Additionally, ROS-induced activation of MAPK pathways (ERK, JNK, and p38) leads to enhanced cell proliferation, apoptosis resistance, and epithelial-to-mesenchymal transition (EMT), contributing to tumour progression in cancer [122, 123]. In metabolic disorders like diabetes, RAGE-ROS signalling disrupts insulin signalling by promoting IRS-1 serine phosphorylation, leading to insulin resistance and β-cell dysfunction. Furthermore, ROS-mediated oxidation of DNA, lipids, and proteins exacerbates cellular damage and accelerates aging and neurodegeneration. This vicious cycle of RAGE-dependent ROS generation and subsequent oxidative stress-driven inflammation creates a self-sustaining loop, amplifying disease progression. Given its central role in oxidative stress and inflammation, targeting RAGE-ROS crosstalk using antioxidants, NOX inhibitors, or RAGE antagonists presents a promising therapeutic strategy for mitigating the pathological consequences of chronic diseases [124, 125].

The most prevalent ROS are hydrogen peroxide ($H_2O_2$) and superoxide ($O_2\bullet-$), which are regular byproducts of several enzymes and metabolic processes. But under the right circumstances, even more hazardous and reactive species such the hydroxyl radical (●OH), singlet dioxygen, and RNS (reactive nitrogenous species) are also produced [126]. Even in healthy mitochondria, the production of ROS is a collateral small activity that cannot be completely eradicated, in addition to

water. It is a natural by product of using oxygen as an electron acceptor ETC. Numerous oxidases and secondary metabolic activities produce $H_2O_2$, whereas the mitochondria and cytoplasm produce trace quantities of superoxide anion. SOD converts superoxide to hydrogen peroxide [127, 128]. The idea that any ROS is bad for cells and that any antioxidant is good is a misconception, even though ROS are often linked to potentially negative consequences. Since, ROS are signal molecules required to control proper metabolism, cell development, differentiation, apoptosis, and autophagy, the production of small levels of ROS under physiological concentrations is a normal process [129]. The activity of a number of enzymes that preserve the intracellular redox balance is intimately linked to the processes that control ROS levels. Pro-oxidant enzymes, which are often oxidases, and antioxidant enzymes, which scavenge reactive oxygen species, are the two main categories. Both groups contribute to the redox equilibrium, respond to different stimuli, and follow different roles; the imbalance in these activities brought on by the first group preponderance is mostly to blame for the emergence of oxidative stress [130, 131].

**CONCLUSION:** The AGE-RAGE axis represents a pivotal molecular link between diabetes and breast cancer, driving chronic inflammation, oxidative stress, and metabolic dysfunction, which contribute to tumor initiation, progression, and metastasis. Persistent hyperglycaemia and insulin resistance in diabetes enhance AGE accumulation, leading to sustained RAGE activation and the induction of key oncogenic pathways such as NF-κB, PI3K/Akt, MAPK, and JAK/STAT. These signaling cascades not only promote cancer cell proliferation, epithelial-to-mesenchymal transition (EMT), and angiogenesis but also remodel the tumor microenvironment (TME) to support immune evasion and therapy resistance. Additionally, diabetes-induced metabolic alterations, including hyperinsulinemia, increased IGF-1 signaling, and the Warburg effect, further exacerbate breast cancer progression by fueling cellular growth and survival mechanisms. The interplay between RAGE signaling and ROS generation perpetuates a vicious cycle of inflammation and oxidative damage, enhancing genomic instability and fostering a tumor-promoting milieu. Given the growing evidence linking diabetes and breast cancer through the AGE-RAGE axis, targeting this pathway emerges as a promising therapeutic strategy. Potential interventions include RAGE antagonists, AGE inhibitors, and lifestyle modifications aimed at reducing AGE accumulation and RAGE activation. Further research is necessary to explore the clinical applications of RAGE-targeted therapies and their efficacy in breaking the pathological connection between diabetes and breast cancer. By elucidating the molecular intricacies of the AGE-RAGE axis, future studies may pave the way for novel therapeutic approaches that mitigate both metabolic disorders and cancer progression, ultimately improving patient outcomes.

**Future Perspective:** As the molecular interplay between diabetes and breast cancer via the AGE-RAGE axis becomes increasingly evident, future research should focus on targeted interventions that disrupt this pathological link. One promising avenue is the development of RAGE antagonists, soluble RAGE (sRAGE), and small-molecule inhibitors that block RAGE-ligand interactions, thereby preventing chronic inflammation and tumor-promoting signaling. Additionally, AGE inhibitors, such as amino guanidine and ALT-711, could be explored for their potential to reduce AGE accumulation and mitigate RAGE activation in both metabolic and cancerous conditions. Given the role of oxidative stress in AGE-RAGE signaling, antioxidant-based therapies, including natural compounds like resveratrol and curcumin, may serve as adjunct strategies to attenuate ROS-driven tumor progression.

Moreover, precision medicine approaches integrating genetic, epigenetic, and metabolic profiling of patients with diabetes and breast cancer could aid in identifying high-risk individuals and tailoring targeted therapies. Clinical studies evaluating the impact of glycemic control on breast cancer incidence and progression are essential to establish metabolic management as a preventive strategy. Additionally, investigating the role of the AGE-RAGE axis in different breast cancer subtypes, particularly triple-negative and hormone receptor-positive tumors, could provide insights into subtype-specific therapeutic interventions.

Lifestyle modifications, including dietary interventions to limit dietary AGE intake and exercise regimens to improve insulin sensitivity, should also be explored as potential non-pharmacological strategies to disrupt AGE-RAGE signaling. Future studies should also focus on the crosstalk between the AGE-RAGE axis and the tumor microenvironment, particularly immune cell infiltration, fibroblast activation, and vascular remodeling, to identify novel therapeutic targets.

Overall, a multidisciplinary approach integrating metabolic regulation, inflammation control, and cancer-targeted therapies is crucial to developing effective treatment strategies for patients at the intersection of diabetes and breast cancer. By further elucidating the molecular mechanisms and clinical implications of the AGE-RAGE axis, future research can pave the way for innovative therapeutic strategies aimed at improving both metabolic and oncologic outcomes.

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