Biomedicine & Pharmacotherapy 162 (2023) 114676

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Review

Metformin and HER2-positive breast cancer: Mechanisms and therapeutic implications

Sara S Bashraheel [a,1], Hadeel Kheraldine [b,1], Sarah Khalaf [c], Ala-Eddin Al Moustafa [b,d,e,*]

[a] QU Health, Qatar University, P.O. Box 2713, Doha, Qatar
[b] College of Medicine, QU Health, Qatar University, P.O. Box 2713, Doha, Qatar
[c] College of Pharmacy, QU Health, Qatar University, P.O. Box 2713, Doha, Qatar
[d] Biomedical Research Center, QU Health, Qatar University, PO. Box 2713, Doha, Qatar
[e] Oncology Department, McGill University, Montreal, Quebec H3A 0G4, Canada

ARTICLE INFO

Keywords:
Metformin
Diabetes
HER2
Breast cancer
HER2/IGF-1R interaction

ABSTRACT

Due to the strong association between diabetes and cancer incidents, several anti-diabetic drugs, including metformin, have been examined for their anticancer activity. Metformin is a biguanide antihyperglycemic agent used as a first-line drug for type II diabetes mellitus. It exhibits anticancer activity by impacting different molecular pathways, such as AMP-inducible protein kinase (AMPK)-dependent and AMPK-independent pathways. Additionally, Metformin indirectly inhibits IGF-1R signaling, which is highly activated in breast malignancy. On the other hand, breast cancer is one of the major causes of cancer-related morbidity and mortality worldwide, where the human epidermal growth factor receptor-positive (HER2-positive) subtype is one of the most aggressive ones with a high rate of lymph node metastasis. In this review, we summarize the association between diabetes and human cancer, listing recent evidence of metformin's anticancer activity. A special focus is dedicated to HER2-positive breast cancer with regards to the interaction between HER2 and IGF-1R. Then, we discuss combination therapy strategies of metformin and other anti-diabetic drugs in HER2-positive breast cancer.

1. Introduction

Breast cancer (BC) remains dubbed as the most common cancer in women. In 2020, more than 2.26 million new BC cases were diagnosed worldwide. Several classification schemes have been developed and utilized for diagnostic, therapeutic, and scientific research purposes over the years. The current classification is based on well-profiled molecular hallmarks and their gene expression patterns. It encompasses five distinct groups: luminal A, luminal B, HER2-positive, basal and normal basal-like [1]. There are several identified risk factors for BC, such as age, family history, reproductive factors (i.e., early menarche, late menopause, etc.), and lifestyle choices such as excess alcohol consumption [2]. Among the different risk factors contemplated, whether in initial causation or disease progression, is type II diabetes mellitus (T2DM). This observation was documented in several scientific investigations that found a strong association between the two conditions, with a notable increased risk of BC in diabetes mellitus patients compared to individuals free of the latter [3–8]. Accumulating epidemiologic data supporting this association prompted scientific research to explore possible shared molecular pathways and advance therapeutic options for the treatment of this malignant disease. Major common genes/pathways that are shared between T2DM and BC include insulin-like growth factor 1 (IGF-1), the secretion of inflammatory adiponectin/leptin, and deficient immune response due to elevated levels of pro-inflammatory cytokines, such as tumor necrosis factor-a (TNF-α) [9,10]. Overall, in T2DM, pro-inflammatory conditions are present due to disrupted glucose metabolism and accompanying hyper-insulinemia, which eventually kickstarts a cascade of tumor-promoting events (6). However, further elucidation of the molecular pathways responsible for the positive association between the two co-morbidities is needed.

HER2 was identified as an important oncogene in the pathogenesis of BC as early as 1987 [11]. The HER2-positive subclass of BC constitutes approximately 20% of all subtypes and is implicated in aggressive phenotype. HER2-positive BC exhibits deregulation and mutation in many key genes that accumulate to enhance tumor aggressiveness and invasiveness, such as TP53, CDK12, PI3KCA, and PTEN [12]. Thus,

* Corresponding author at: College of Medicine, QU Health, Qatar University, P.O. Box 2713, Doha, Qatar.
E-mail addresses: ala-eddinalmoustafa@mcgill.ca, aalmoustafa@qu.edu.qa (A.-E.A. Moustafa).
[1] Authors contributed equally to the work.

https://doi.org/10.1016/j.biopha.2023.114676
Received 16 February 2023; Received in revised form 1 April 2023; Accepted 6 April 2023
Available online 8 April 2023

several targeted therapies have been developed and utilized for the treatment of this disease [13]. Limited data exists on the link between HER2-positive BC and its association with T2DM [14–16]. Nevertheless, due to the shared molecular pathways between the two diseases, the possible use of T2DM medications in HER2-positive BC, with a particular focus on metformin, has been the focus of several studies.

Metformin is a multi-faceted drug in terms of its various uses in different ailments, either for their prevention or treatment. Along with its primary role in T2DM management, metformin has been utilized to treat other conditions including diabetic nephropathy, cardiovascular diseases and polycystic ovary disease. More recently, Metformin has been proposed as a preventive or therapeutic agent against cancer [17]. Multiple studies have investigated the spectrum of its effects on HER-positive BC, in experimental [18–20], epidemiological [21], or large-scale clinical trial settings [22–25].

In this review, we attempt to elucidate the most recent advances and scientific efforts dedicated to the role of metformin as a potential therapeutic agent in HER2-positive BC. First, we will discuss the association between diabetes and cancer, including molecular interactions between IGF-1R and HER2 in BC. Then, the potential role of metformin and other T2DM drugs in the management of HER2-positive BC will be reviewed. Lastly, we conclude with a short summary on the topic and future perspective.

2. Diabetes and human cancers including breast

Collectively, diabetes and cancer are the leading causes of death worldwide. Cases of diabetes and cancer have been steadily increasing over the past few decades. According to the international diabetes federation reports in 2021, around 6.7 million deaths account for diabetes, with 537 million adults living this disease worldwide [26]. While, in 2020, about 18.1 million newly diagnosed cases and 10 million deaths are attributed to cancer, of which BC represents 2.26 million newly diagnosed and 685,000 global mortality cases [27]. As mentioned above, several reports have shown that there is an increased risk of various cancers, including colon, breast, pancreas, colorectal, endometrial, liver, and bladder in diabetic patients [28]. Additionally, the effect of diabetes risk reduction diet (DRRD) on BC was investigated, and found that adherence to DRRD decreased the risk of BC [OR 0.93, 95% confidence interval (CI), 0.89–0.98] [29,30]. Furthermore, a retrospective study in Louisiana reported a significant association between diabetes and BC subtypes, including Luminal A, triple-negative, and HER2-positive [31].

Diabetes has also been associated with aggressive tumor prognosis, progression, and mortality [32]. More specifically, diabetic patients have elevated levels of bioavailable IGF-1 which increases their risk of evolving malignancies such as breast, colorectal, and prostate cancer [33,34]. Recently, an investigation involving 26,968 BC patients, with 11.6% diabetic cases, showed that the probability of BC and diabetes co-occurrence raised over time. Diabetic patients had a higher chance of diagnosis with stage III-IV BC than non-diabetic ones (OR 1.14, 95% CI 1.03–1.27; and 1.17, 95% CI 1.00–1.38). Additionally, diabetic women aged 45–69 are more likely to have screen-detected BC (OR 1.13, 95% CI 1.02–1.26) [35]. Furthermore, it has been reported that BC patients with diabetes had a higher 5-year mortality risk than those without diabetes [36]. These observational studies have been supported by several experimental one. An in-vivo comparison investigations conducted on mice fed with either high or low glycemic index food showed rapid development of BC with severe tumor burden in mice fed with high glycemic index food [37]. In fact, aggressive tumor proliferation is linked to high glucose concentration in the tumor microenvironment (TME), which is the main source of energy for tumor growth [38,39]. Therefore, any antidiabetic drugs that lower glucose levels, such as metformin, could be a potential cancer therapy.

Diabetes and cancer share common risk factors, including aging, obesity, smoking, and alcohol consumption. The risk of having diabetes and cancer increases with age. The majority of cancer incidence, approximately 70%, occurs among individuals aged over 50. Only 5% of worldwide cancer cases occur in children and adolescents below the age of 15 [40]. While US statistics show the increasing prevalence of diabetes with age, 2.2% among the 20–24 age group, 6% among the 35–39 age group, 11% among the 45–49 age group, 17% among the 55–59 age group, 21% among the 65–69 age group, and 24% among the 75–79 age group [41]. The prevalence of diabetes and cancer is slightly higher in men than in women [41,42]. Moreover, around 4% of all cancer cases in 2012 were linked to high BMI. Several site-specific cancers have also been linked to high BMI, including postmenopausal breast, ovarian, kidney, liver, colorectal, gallbladder, pancreas, endometrial, gastric cardia, and thyroid cancers, as well as oesophageal adenocarcinoma and multiple myeloma [43]. Similarly, there is a strong association between T2DM and high BMI representing the association of obesity with both cancer and diabetes [44–46]. In addition, smoking tobacco accounts for two-thirds of lung cancer deaths worldwide; however, at least 19 other types of cancers are associated with smoking, including larynx, upper digestive, bladder, kidney, pancreas, leukemia, liver, stomach, and uterine cervix [47]. Smoking is also reported as an independent risk factor for diabetes, where active smokers have a 40% higher risk of developing diabetes than non-smokers [48–50]. In 2016, 4.2% of cancer deaths worldwide were attributed to alcohol consumption. The risk of cancer increases with increased consumption of alcohol, and it can cause a variety of cancer types, including breast [47]. On the other hand, moderate consumption of alcohol is associated with reduced diabetes risk, while excess consumption is a risk factor for diabetes [51–53].

Several anti-diabetic drugs, such as thiazolidinedione (TZD), insulin, insulin analogs, and metformin, have also shown an effect on cancer risk and progression. TZD acts as a peroxisome proliferator-activated receptor γ (PPARγ) agonist to induce cell apoptosis by increasing the level of apoptotic molecules and inhibit cancer cell invasion by blocking MEK-ERK signaling in colorectal and bladder cancers [54,55]. One study showed that diabetic patients prescribed with TZDs had a significantly lower risk of BC [56]. Additionally, a meta-analysis on pioglitazone and rosiglitazone TZDs showed a strong association between pioglitazone intake and reduction in BC, while no association was observed in the case of rosiglitazone [57]. However, a recent meta-analysis of studies published before 2016 reported no significant association between BC and TZDs intake among diabetic women [58]. Furthermore, insulin and insulin analogs are associated with increased cancer risk due to hyperinsulinemia, but these are usually prescribed in the advanced stage of T2DM [36,59,60]. All these studies show clearly that there is a strong association between diabetes and cancer initiation and/or progression. Therefore, based on the shared molecular mechanisms between the two ailments, metformin and other diabetes drugs may have an important role in the management of human cancers, including breast. This will be discussed in the section below.

3. Metformin and human cancers including breast

There is contradicting evidence on the effect of metformin on cancer risk in T2DM patients. In 2017 a systematic review of metformin and cancer risk studies indicated that only 3 studies out of 46 were rated as low or unlikely for bias domains, including outcome, exposure, control selection, baseline confounding, time-dependent confounding, immortal time, missing data, and censoring methods. Therefore, the authors suggested that there is insufficient evidence supporting the association between metformin and cancer risk in T2DM patients [61]. Accordingly, two meta-analysis reports, one involving 12 studies and 16,230 participants and the other involving 11 studies and 838,333 participants, both proposed no association between metformin consumption and BC incidents in T2DM patients (Odd Ratio OR = 0.93; 95% Confidence Interval CI, 0.85–1.03; I^2 = 35% and Relative Risk RR 0.964; 95% CI= 0.761–1.221; p = 0.761)[62,63]. However, both reports showed a significant decrease in BC all-cause mortality (Hazard Ratio HR = 0.55;

95% CI, 0.44–0.70; I^2 = 81% and RR= 0.652; 95% CI= 0.488–0.873; p = 0.004) [62,63]. A recent systematic review investigated the cancer risk of T2DM patients treated with metformin. The meta-analysis included data from 10,695,875 T2DM patients and 145,108 cancer cases which met the study criteria. T2DM patients who used metformin had a significantly decreased risk of cancer compared to those who never used metformin (OR=0.70, 95% CI=0.65–0.76). Further analysis comparing metformin with other anti-diabetic drugs revealed a statistically decreased cancer risk for T2DM patients under the metformin course (OR=0.80, 95% CI=0.73–0.87). Therefore, metformin may play an independent role in reducing cancer risk in T2DM [64].

Additional analysis on metformin and BC association, with a focus on potential biases, was performed on seven studies in postmenopausal women with diabetes (OR 0.83, CI 0.71–0.97). The analysis confirms the protective effect of metformin on BC risk where longer use of Metformin show a stronger association (OR = 0.75. 95% CI 0.62–0.91) [65]. Moreover, consumption of metformin before cancer diagnosis is associated with a reduced risk of BC (OR = 0.821, 95% CI=0.726–0.928, p = 0.002) [66].

Furthermore, early prescription and compliance to metformin resulted in a 25% reduction in cancer risk (OR= 0.75, 95% CI= 0.67–0.84) than late prescription and non-compliance [67]. Adherence to metformin reduces tumor-specific mortality in colorectal, endometrial, and BC patients. More specifically, consideraing a baseline of 12 months period of adherence to metformin, a 10% increase in adherence reduced tumor-specific mortality in women with colorectal cancer (adjusted HR = 0.94), endometrial cancer (adjusted HR = 0.95; 95% CI= 0.90–0.99), and BC (adjusted HR = 0.95; 95% CI= 0.93–0.97) [68].

Metformin consumption upon diagnosis with lung cancer has been associated with improved survival (HR = 0.79, 95% CI= 0.72–0.87) and progression-free survival (PFS; HR = 0.62, 95% CI: 0.39–0.96)[69]. The same was observed in diabetic liver cancer patients using metformin (HR = 0.64; 95% CI, 0.42–0.97; p = 0.035) [70]. Additionally, Metformin improves cancer-specific survival (CSS) (n = 533), RFS (n = 623), and OS (n = 1936) indicators in patients with colorectal cancer [71]. However, a meta-analysis conducted using randomized controlled trials (RCTs) investigated the influence of metformin on the survival of non-diabetic BC patients and concluded that there is no association between the use of metformin and improved progression-free survival (PFS, hazard ratio [HR]: 1.00, 95% confidence interval [CI]: 0.70–1.43, p = 0.98; I^2 = 32%) or overall survival (OS, HR: 1.00, 95% CI: 0.71–1.39, p = 0.98; I^2 = 0%). The analysis included five phase II RCT studies with a total of 396 non-diabetic BC patients [72]. In addition, Tadel et al. used different cancer cell lines (MCF-7, MCF-7/DX, A549, CCRF/CEM, THP-1, NHDF) to investigate the impact of metformin on cell proliferation. All cell lines used had decreased cell proliferation with increasing doses of metformin confirming its anticancer effect [73].

Furthermore, combination therapy studies on metformin and other medications showed an increased protective effect on cancer risk, including breast [74–76]. Usage of cardiovascular drugs such as aspirin and statin had no link to cancer incidents, while a combination of these drugs along with metformin showed an augmented protective association with lung cancer risk and mortality [74,75]. Similarly, Sung et al. observed a significant decrease in cancer risk when aspirin and metformin were used independently and an elevated reduction in risk of cancer (HR 0.53, 95% CI 0.45–0.63) when both aspirin and metformin were used together [76]. Other combinational therapies showed a synergistic or significantly enhanced anticancer effect in-vitro and in-vivo on various cancer types, including breast [77–80]. A recent study showed a synergistic effect of metformin and copper chelator against Triple Negative Breast Cancer (TNBC). Through AMPK activation, whereby metformin can lead to the phosphorylation and stabilization of CTR1, which translocates copper and activates its oncogenic pathway [81]. Early prescription of metformin monotherapy or combination therapy is associated with 34% (OR, 0.66; 95% CI, 0.51–0.83) and 25% (OR, 0.75; 95% CI, 0.64–0.88) lower cancer risk, respectively. Therefore, Early prescription of metformin monotherapy or combination therapy is recommended [67]. Table 1 summarizes the main research outcomes of proposed metformin combination therapy.

Herein it is important to note that Metformin can elicit anticancer effect directly as well as indirectly by reducing the level of glucose in the TME [82]. Both direct and indirect effects of metformin involve AMPK-dependent and AMPK-independent mechanisms (Fig. 1). The AMPK-dependent pathway involves the activation of AMPK which inhibits GATOR2 complex by phosphorylation of its component WDR24 that leads to the downregulation of mTOR, including p70S6K/pS6 proteins [83–85]. Further, activation of AMPK is achieved by inhibition of cancer cell mitochondrial complex I, which leads to the reduction in ATP level and increase in AMP/ATP level, thereby activating the glycolytic pathway and LKB1, which in turn phosphorylates AMPK [86,87]. The AMPK-independent pathway of metformin works by reducing the level of blood glucose and IGF-1 ratio, which inhibits PI3K/AKT/mTOR signaling pathways, thereby inhibiting tumor proliferation [84]. Indeed, studies showed that metformin decreases tumor formation in-vivo as well as cell invasion and growth in-vitro partially by activating PP2A [88]. Another AMPK-independent mechanism of metformin is via cyclin D1 downregulation, that upregulates P53 to promote apoptosis and inhibit cell proliferation in BC cells [89]. Metformin can also stimulate cancer cell invasion and proliferation by increasing KIBRA and FRMD6 expression patterns, which leads to YAP phosphorylation, thus inhibiting its translocation and binding to TEAD [90]. In fact, a recent study found that metformin inhibits cell proliferation and invasion in drug-resistant BC cells through an AMPK-independent approach [90]. In this regard, a recent in-vivo and in-vitro study by Liu et al. on Tamoxifen- and paclitaxel-resistant cells showed that metformin can increase cell membrane localization of the cell polarity protein Scribble (SCRIB), which enhances its interaction with MST1 and LATS1 and suppresses Yes-associated protein (YAP) nuclear localization and transcriptional activity [91]. In primary BC cells (PBCCs), metformin plays an essential antitumor role by suppressing the MMP-9 expression via inhibiting the activity and nuclear translocation of NF-kB [90].

On the other hand, Metformin can induce apoptosis of TNBC cells by inhibiting PI3K/Akt signaling and STAT3 activity and decreasing the expression of X-linked inhibitor of apoptosis protein (XIAP), thus increasing TNBC sensitivity to TRAIL [92]. This was confirmed in another study that demonstrated the role of Metformin in upregulating the production of endogenous TRAIL and stimulating TRAIL-mediated apoptotic pathway in TNBC [93]. Other investigations have also shown that metformin can reverse TME immunosuppression in TNBC [94,95]. More specifically, Metformin increases the expression of JNK, thereby activating the JNK signaling pathway, and increasing CD4 + and CD8 + Tumor-Infiltrated Lymphocytes (TILs) in the TME of TNBC. In addition, the functional phenotype of TILs is increased and associated with the JNK pathway, where the exhausted phenotype of TILs is suppressed through the AMPK/mTOR pathway [95]. A recent study identified the mechanism through which metformin reduces TNBC growth by targeting its glucose metabolism [96]. Metformin downregulates several glucose transporter proteins, including GLUT1, and attenuates the expression of over 20 genes involved in glucose metabolism [96].

Nevertheless, the associations between Metformin consumption and ER+ BC risk have been contradictory, with some studies suggesting a protective effect against ER+ BCs and others linking Metforming with increased incidents of ER+ BC [97]. Hampsch et al. investigated the effect of Metformin on dormant ER+ BC and suggested that it enhanced dormant ER+ BC cell survival through AMPK activation [98]. Thus, further investigations are needed to elucidate the role of Metformin and its mechanism of action on ER+ BC.

4. Molecular interactions between IGF-1R and HER2 in BC

Insulin growth factor receptor type 1 (IGF-1R) is a cell-surface trans-

Table 1
Outcomes of combination therapy of metformin.

Ref.	Combination Therapy	Outcome	Cancer Type	Study type
[76]	Aspirin and metformin	Reduced cancer risk significantly compared to single therapy.	Various	Meta-analysis
[77]	Vemurafenib and metformin	Synergistic anticancer effects were evaluated using MTT assay and colony formation assay. Suppressed the progression of ATC cells growth by inducing significant apoptosis.	Anaplastic thyroid cancer	*In-vitro*: ATC cells
[78]	Pioglitazone and metformin	Cancer progression is prevented by downregulation of the expression levels of oncogenes, AKT3, CHUK, CDC42, EIF4E, HIF1A, IKBKB, ILK, mTOR, PIK3CA, PIK3CG, PLD1, PRKCA, and RICTOR genes, and upregulation of expression levels of tumor suppressor genes, DDIT4, DDIT4L, EIF4EBP1, EIF4EBP2, FKBP1A, FKBP8, GSK3B, MYO1C, PTEN, ULK1, and ULK2.	Anaplastic thyroid cancer	*In-vitro*: SW1736 and C643 ATC.
[79]	Aspirin and metformin	Enhanced 4T1 cell apoptosis through secretion of TGF-β1.	Breast cancer	*In-vitro*: Murine breast cancer 4T1 cell
[99]	Crocin and metformin	Improved anti-metastatic BC therapy.	Metastatic breast cancer	*In-vitro*: 4T1 cell line *In-vivo*: murine breast cancer model
[100]	Chemotherapy and metformin	Does not improve the progression-free survival (PFS) and overall survival (OS) among women with metastatic BC.	Metastatic breast cancer	Meta-analysis
[80]	Formononetin and metformin	Enhanced cell growth inhibition, and the induction of apoptosis in MCF-7 cells mediated by the ERK1/2 signaling pathway.	Breast cancer	*In-vitro*: MCF-7 cells
[101]	Surgery and metformin	Reduced mortality particularly in the HT+ /HER2 Tx-group.	Breast cancer	Meta-analysis
[102]	Fluoro-2-deoxy-D-glucose, doxorubicin and metformin	Increased phospho-AMPK but decreased phospho-AKT and phospho-ERK expressions.	Breast cancer	*In-vitro*: BT474, SKBR3, MDA-MB-453 and MDA-MB-468 cells
[103]	Tamoxifen and metformin	Synergistically inhibit cell proliferation, DNA replication and induce apoptosis via BAX/BCL-2 apoptotic pathway and AMPK/mTOR/p70S6 growth pathway.	ER-positive breast cancer	*In-vitro*: MCF-7 and ZR-75–1 *In-vivo*: nude mice
[104]	Paclitaxel and metformin	Synergistically induce higher cytotoxicity and apoptosis through Toll-like receptor (TLR) signaling by activation of TLR-MyD88-ERK.	Breast cancer	*In-vitro*: 4T1 cells *In-vivo*: BALB/c mice
[105]	Everolimus and metformin	Additive anti-proliferative and colony inhibitory effect by repressing mitochondrial respiration and mTOR signaling.	Breast cancer	*In-vitro:* MCF-7, MDA-MB-231 and T47D
[106]	Vitamin D3 and metformin	Synergistic antitumor activity involving mTOR signaling pathways by activating the expression of cleaved caspase-3, BAX, and p-AMPK, and inhibiting the expressions of p-BCL-2, c-Myc, p-IGF-1R, p-mTOR, p-P70S6K, p-S6.	Breast cancer	*In-vitro*: MDA-MB-231 cells
[107]	Curcumin and metformin	Reduced tumor proliferation and growth, induced apoptosis, and inhibited angiogenesis.	Breast Cancer	*In-vivo*: BALB/c mice *In-vitro*: EMT6/P, MCF-7, T47D and Vero
[108]	Standard therapy and metformin	The addition of metformin vs placebo to standard BC therapy had no significant effect on invasive disease-free survival.	Breast cancer	Clinical trial phase III
[109]	Radiotherapy and metformin	Improved tumor response to radiotherapy in cancer and diabetes mellitus patients, enhanced short-term efficacy and overall survival.	Various	Meta-analysis
[110]	Cisplatin and metformin	Metformin downregulates RAD51 expression and enhances cisplatin's anticancer effect	TNBC Breast Cancer	*In-vitro:* Hs578T and MDA-MB-231 cells *In-vivo:* 4T1 murine model
[111]	Resveratrol and metformin	Synergistic inhibition of cancer progression.	TNBC Breast Cancer	*In-vitro:* MDA-MB-231 cells
[81]	Copper chelator TTM and metformin	Metformin activates AMPK which inhances CTR1-copper signalling and its downstream	TNBC Breast Cancer	*In-vivo:* Xenografted mouse models

(*continued on next page*)

Table 1 (*continued*)

Ref.	Combination Therapy	Outcome	Cancer Type	Study type
		oncogenic pathway.		

membrane receptor tyrosine kinase (RTK) composed of two alpha and two beta subunits [112]; IGF-1R binds insulin growth factor types I and II to insulin in the extracellular alpha domain with high affinity [112]. Moreover, its beta subunits contain an intracellular tyrosine kinase catalytic domain. The IGF-1R signaling pathway is involved in the development of different types of cancers, such as breast, which makes it a promising target in cancer treatment [113,114]. Fig. 2.

Promoting cancer progression through IGF-1R survival cascade starts with ligand binding, which causes receptor conformational change and activates IGF-1R intrinsic kinase action via autophosphorylation, as the extracellular alpha chain triggers tyrosine kinase phosphorylation of the intracellular beta chain [112]. The autophosphorylation of IGF-1R activates multiple signaling chains, such as the mitogen-activated protein kinase (MAPK), the phosphoinositide-3 kinase (PI3K) and the JAK/STAT pathways, thereby increasing cell survival, proliferation, and differentiation as well as inhibiting apoptosis [115,116]. In detail, when IGF-1R is phosphorylated, it binds and phosphorylates different scaffold proteins; insulin receptor substrate proteins (IRS1/2/4) and SHC1, which in turn become phosphorylated and bind to effectors. The IRS1/2/4 proteins bind and phosphorylate PI3K through its p85 subunit, resulting in the formation of phosphoinositol phosphate3 (PIP3), which in turn activates the AKT/mTOR signal transduction pathway. The PIP3 pathway is correlated with cell growth as well as suppressing apoptosis. Thus, cell proliferation, differentiation, and increased protein synthesis occur, which are the major hallmarks of tumorigenesis [115,117].

IGF-1R-activated IRS1/2/4 proteins also bind to the GRB-2/SOS complex, which in turn stimulates the replacement of GDP with GTP of RAS protein, resulting in activating RAF, ERK, and MAPK pathways. The extracellular signal-regulated kinase 1 and 2 (ERK1/2) pathway activates different transcription factors in the nucleus, such as c-Jun and c-Myc, to inhibit apoptosis and initiate mitosis. Additionally, IGF-1R can also stimulate the Janus kinase, signal transduction and transcription activator pathway (JAK/STAT). Then, phosphorylated STAT enters the nucleus and promotes cell stemness and epithelial-mesenchymal transition (EMT) [118].

On the other hand, IGF-1R signaling interacts with other receptor tyrosine kinases of growth factors family members, such as EGFR, VEGF, and HER2. Specifically, the IGF-1R and HER2 involve similar signaling pathways. HER2 is amplified in 15–20% of total BC cases, which is correlated with poor prognosis and aggressive tumors. HER2 represents a favorable drug target in these tumors, either by humanized monoclonal antibodies (mAbs) like trastuzumab or by small-molecule tyrosine kinase inhibitors (TKIs) like lapatinib [119,120]. However, innate and acquired resistance toward these treatment strategies is still a limitation in HER2-positive BC. Therefore, understanding the molecular interactions between IGF-1R and HER2 signaling might be beneficial in targeting HER2-amplified BCs.

The extracellular domain of HER2 cannot bind with ligands, thus, it is activated by homo or heterodimerization with other ligand-activated growth factor receptors, including but not limited to EGFR and IGF-1R [121]. This mode of HER2 activaition is considered one of the most important mechanisms of developing drug resistance in HER2-amplified cancers [122]. Similar to IGF-1R, activating HER2 triggers downstream signaling pathways, such as PI3K/MAPK, AKT/mTOR, and STAT pathways, which are regulated by several partners, such as SHC1 and GRB-2 [123]. These are key pathways in tumorigenesis that start by promoting cell growth, proliferation, dedifferentiation, survival, angiogenesis; then initiates EMT and consequently cell invasion, which are likely to occur in HER2-positive cancer [123].

HER2 is activated and phosphorylated by forming a heterodimer with IGF-1R. This interaction is strongly correlated with resistance to mAbs that target and inhibit HER2, such as trastuzumab [119,124].

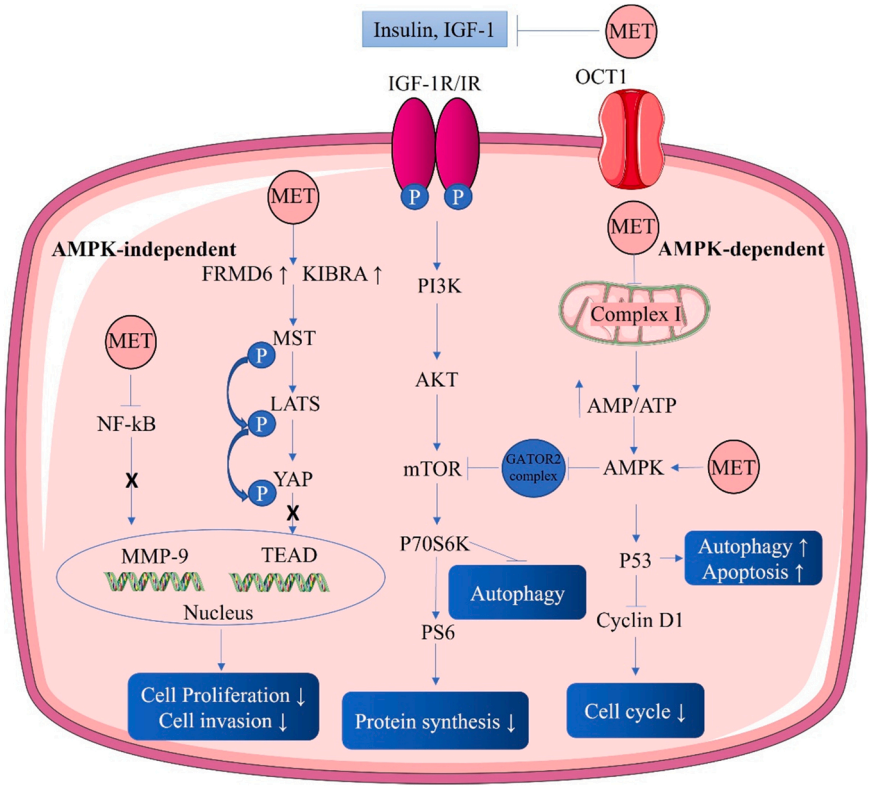

Fig. 1. AMPK dependent and independent mechanism of action of metformin.

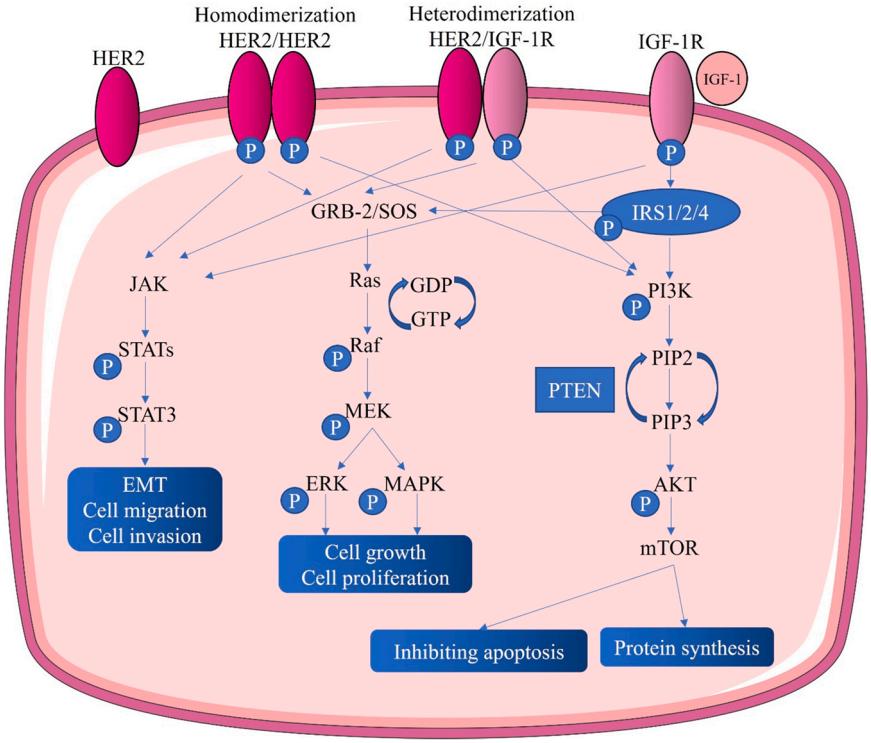

Fig. 2. IGF-1R signaling and its crosstalk with HER2.

Interestingly, HER2 tends to form heterodimers with IGF-1R in trastuzumab-resistant cells but not in trastuzumab-sensitive cells. However, inhibiting this heterodimerization does not change HER2 phosphorylation, it re-sensitizes the cells to trastuzumab treatment and decreases cell viability [124]. Moreover, resistance to trastuzumab is associated with IGF-1R overexpression in HER2-positive BCs [119,121]. Further, IGF-1R signaling can also increase the invasive potential of HER2-overexpressing BC cells by activating Src and focal adhesion kinase (FAK). This promotes the expression of forkhead box protein M1 (FoxM1), leading to increased cell invasion [120]. Therefore, various studies suggest co-targeting HER2 and IGF-1R as promising strategies to enhance drug efficacy in HER2-positive BC to overcome mAbs resistance [119,121,125]. The most common IGF-1R targeting strategies include: IGF-1R monoclonal antibodies (mAbs), IGF-1 and IGF-2 mAbs, IGF-1R tyrosine kinase inhibitors, and proteolysis targeting chimeras (PROTACs) [126,127].

It is also important to highlight that IGF-1R can also interact with other growth family receptors, most importantly EGFR. Both receptors share downstream signaling pathways, such as AKT and MAPK. EGFR is hyperactivated in most types of cancer, resulting in cell proliferation, differentiation, migration, and invasion. Resistance towards EGFR-targeted therapies is strongly linked with its crosstalk with IGF-1R [128,129], as blocking EGFR subsequently activates IGF-1R signaling pathways as a compensation [128]. Thus, co-targeting IGF-1R and EGFR is shown to be a promising approach to treating metastatic cancer [130]. In addition, inhibiting IGF-1R may resensitize cancer cells to anti-EGFR treatments [131]. IGF-1R interacts with vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and fibroblast growth factor receptor (FGFR), which promotes cancer progression and tumorigenesis [132]. The crosstalk between IGF-1R and the different RTKs (HER2, EGFR, VEGFR, PDGFR, FGFR) makes it an attractive target in cancer treatment. Therefore, blocking IGF-1R stops its downstream signaling pathway, while also inhibiting its interaction with other RTK family members.

5. Potential role of metformin and other T2DM drugs in the management of HER2-positive BC

The potential role of metformin in the management of HER2-positive BC has been intensively explored by different in-vitro and in-vivo studies, due to the relationship between diabetes and cancer occurrence. Several clinical trials sought to draw a definite conclusion on metformin effects in HER2-positive BC patients either as mono treatment or in combination with other treatment strategies. However, the conclusion was influenced by several factors, such as patients' diabetes status, genotyping, type of standard treatment strategy used, etc. Table 2.

In-vitro examinations revealed that metformin mono treatment inhibits cell proliferation and colony formation in HER2-positive SKBR3 and BT474 cell lines, as well as downregulates HER2 expression and phosphorylation [133,134]. It also results in partial cell cycle G1 arrest [135,136] and induction of apoptosis via inhibiting HSP90 [133]. Metformin has been shown to exhibit protective and risk-reducing effects against HER2-positive BC, as it inhibits HER2 overexpression by blocking p70S6K1, an mTOR effector in HER2-positive BC cell lines [136] (Fig. 1). The mTOR/p70S6K1-sensed ROS status in HER2-positive BC cell lines was highlighted as an important biomarker and target to predict metformin anticancer effects, in addition to HER2 oncogene overexpression [136]. At lower concentrations, metformin re-sensitizes resistant cells to anti-HER2 treatments, such as lapatinib and it augment its effecacy [142]. Lapatinib resistance usually occurs within 12 months of treatment. In addition, lapatinib and other anti-HER2 drugs exhibit cardiac toxicity due to the role of HER2 in regulating the cardiac cell function [143]. Therefore, combining Metformin treatment with lapatinib can simoultaneosly inhibit HER2 signaling pathway along with activating AMPK; which protects from adverse cardiac effects associated with anti-HER2 drugs [142]. Additionally, combining Metformin with trastuzumab, which is the first-line treatment of HER2-positive BC, inhibits the proliferation and self-renewal of cancer stem and progenitor cells in HER2-positive BC cell lines [137]. Also, metformin has cardioprotective effects through activating AMPK and induction of

Table 2
Summary of in-vitro and in-vivo studies that investigated the anticancer effects of metformin and other anti-diabetic drugs on HER2-positive BC.

In-vitro studies			
Treatment	Model	Outcome	Reference
Metformin	SKBR3 and BT474 cells	Cancer inhibition Resensitzing cells to treatment and reverting hyperinsulinemia	[133,134],[135, 136]
Metformin + Trastuzumab	BC stem cells	Cancer stem and progenitor cell inhibition	[137]
Metformin + Phenformin	Murine HER2-positive MMTV-Erbb2 cells	Cell apoptosis and necrosis	[138]
Metformin	Co-culture of endothelial cells and HER2-positive BC cells	Anti-angiogenesis	[134]
Metformin + phenphormin	Co-culture of white adipose tissue progenitor cells and HER2-positive BC cells	Anti-angiogenesis	[138]
In-vivo studies			
Treatment	**Model**	**Outcome**	**Reference**
Metformin + phenphormin	Orthotopic xenograft mice model	Inhibition of local and metastatic HER2-positive BC	[138]
Metformin	HER-2/neu transgenic mice	Life span increase	[139,140]
Diabenol	HER-2/neu transgenic mice	Life span increase	[141]

catabolism, thus protecting from cardiac adverse effects such as cardiomyopathy associated with anti-HER2 treatments [142]. Another in-vitro examination showed that Metformin and phenformin; another biguanide antidiabetic drug, increase cell apoptosis and necrosis of HER2-positive BC cell lines, most likely by activating AMPK signaling. The combined action of Metformin and phenformin was also investigated in-vivo, where it was shown to inhibit local and metastatic growth of HER2-positive BC [138]. Metformin is also known for its anti-HER2-induced-angiogenic effects, which are mediated by inhibiting HER2/HIF-1α/VEGF secretion axis. More specifically, it inhibits micro-vessel density and leaking [134]. *In-vivo* studies revealed that long-term exposure to Metformin treatment can increase the life span of HER2-positive mice [139]. Metformin also results in a deceleration of aging and protects mice with HER2 oncogene from developing tumors, leading to the assumption that it might prevent age-related diseases, including cancer [140]. Other anti-diabetic drugs, such as diabenol (a sulfonylurea antidiabetic drug), show geroprotecting effects and prolong the lifespan of transgenic HER2-positive mice. Diabenol, which increases insulin sensitivity, might prevent age-associated diseases like cancer by reducing the levels of insulin and IGF [141].

The proposed mechanisms of action of metformin anticancer effects include:

- Reverting hyperinsulinemia [135,136].
- Inhibiting cancer cell growth [135,136].
- Downregulating HER2 expression and phosphorylation [134–136].
- Downregulating cyclin D1 and E2F1 expression [135].
- Inhibiting MAPK, AKT, and mTOR activity [135,144].
- Activating AMPK which is associated with mTOR inhibition [136, 142].
- Inhibiting IGF-1R signaling [144].
- Blocking cell cycle progression [135,144].

The outcome of clinical trials that recruited Metformin as a potential anti-HER2-positive BC treatment varied thus far between diabetic and non-diabetic patients. For instance, a clinical trial that included diabetic women with HER2-positive BC treated with Metformin and thiazolidinediones; another anti-diabetic drug, showed better clinical outcomes and survival in the Metformin group [21]. This trial suggests that survival rates in these patients can be improved according to the chosen anti-diabetic adjuvant treatment [21]. Another study investigated the relationship between diabetes, Metformin use, and BC outcome in post-menopausal women with diabetes. The study revealed that Metformin decreases the risk of the HER2-positive BC but not the risk of other BC subtypes [145]. Further, another trial included 1013 BC patients with diabetes divided into two groups; with or without Metformin treatment. The conclusion stated clearly that the Metformin-treated group had a lower HER2-positive rate [146]. Another study examined the clinicopathological features of 711 BC patients with diabetes. However, this trial showed that Metformin did not change the expression of HER2 in those patients, but it significantly decreased the risk of lymph node metastasis [147].

Moreover, a phase II clinical trial evaluated the safety and efficacy of adding Metformin to neoadjuvant anthracycline/taxane-based chemotherapy and trastuzumab in women with early HER2-positive BC. A total of 57 patients were enrolled in this trial. The combination therapy was well-tolerated with no significant toxicity compared to standard care. However, as this study was underpowered with a low number of recruited patients, it was not possible to firmly conclude Metformin efficacy in HER2-positive BC, as larger investigations are warranted [148]. Further, a phase III randomized clinical trial included a total of 3649 non-diabetic patients with a high risk of nonmetastatic BC receiving standard therapy. Compared to a placebo, adding metformin to standard treatment protocol did not enhance invasive disease-free survival rates and overall survival. Interestingly, a significant association was found between achieving a pathological complete response by Metformin treatment and the presence of the rs11212617 allele in these patients [108]. It is necessary to indicate that this allele which is located on the gene encoding for the insulin receptor substrate 1 (IRS1), was previously shown to regulate glucose metabolism and cellular growth, and is strongly associated with metformin treatment success in T2DM patients [149]. In fact, different clinical trials showed the importance of C allele-containing rs11212617 genotype presence as a predicting biomarker for achieving maximum anti-tumor effects of Metformin in non-diabetic HER2-positive BC patients [24,108,150]. Table 3.

By reviewing previous clinical trials, it appears that the clinical benefits of Metformin in the treatment of HER2-positive BC is affected by the combination therapy approach used and the presence of the rs11212617 allele. Also, the patient's diabetic status might interfere with the outcome. Thus, more studies are warranted to optimize Metformin use as a part of combination therapy in HER2-positive BC before drawing a conclusion regarding its anticancer effects. Despite contradictory data reported in the literature, including Metformin in HER2-positive BC treatment regimens might add benefits and enhance its anti-HER2 effects [151].

6. Conclusion and future perspective

Metformin, a drug used in the treatment of T2DM, has recently drawn attention due to its anticancer effects on different types of cancer, mainly BC. Metformin targets different key pathways related to cell proliferation, invasion, migration, and apoptosis which are the hallmarks of cancer. Additionally, it has been shown that metformin indirectly inhibits HER2 signaling cascade. Due to the crosstalk between

Table 3
Summary of clinical trials that investigated the anticancer effects of Metformin on HER2-positive BC.

Study type	Treatment	Patients	Outcome	Ref
Observational	Metformin + Thiazolidinedione	1983 diabetic and non-diabetic patients with HER2-positive BC	Enhanced clinical outcomes	[21]
Observational	Metformin	3401 post-menopausal women with diabetes	Decreased HER2-positive BC risk	[145]
Retrospective study	Metformin	1013 diabetic BC patients and 4621 non-diabetic BC patients	Lower HER2-positive rate	[146]
Retrospective study	Metformin	89 diabetic patients with BC	No change in HER2 expression	[147]
Phase II clinical trial	Metformin + trastuzumab or Metformin + chemotherapy	98 HER2-positive BC patients	No significant toxicity but no conclusion on the efficacy	[148]
Phase III clinical trial	Metformin	3649 non-diabetic patients with a high risk of BC	No impact on disease-free survival	[108]

IGF-1R and HER2 signaling pathway. Numerous investigations focused on the impact of Metformin on HER2-positive BC in-vitro, in-vivo, and in clinical trials, either as monotherapy or in combination with other anti-HER2 drugs and chemotherapy. These studies show clearly that Metformin inhibits cancer growth and metastasis in HER2-positive BC cell lines as well as in HER2-positive mice models. Nevertheless, in patients, Metformin is well-tolerated at high doses and shows protective effects against developing HER2-positive BC risk. However, a lack of its anticancer efficacy was observed in clinical trials, with no significant impact on survival rates. It is fair to mention that some of the studies reported in this review were observational in nature and do not prove causality. This warrants more trials with increased sample size, taking into consideration the diabetic status, genotyping, and rs11212617 allele presence in patients. Furthermore, exploring the outcome of novel anti-HER2 drugs in combination with Metformin in HER2-positive BC might be the key to gain the desired anticancer effects.

CRediT authorship contribution statement

Ala-Eddin Al Moustafa: Conceptualization. **Sara Bashraheel, Hadeel Kheraldine**, **Sarah Khalaf:** Writing – original draft preparation. **Ala-Eddin Al Moustafa:** Supervision. **Sara Bashraheel, Hadeel Kheraldine, Ala-Eddin Al Moustafa:** Writing – review & editing.

Conflict of interest

The authors declare that there are no conflicts of interest.

Acknowledgments

The research work in the laboratory of Professor Ala-Eddin Al Moustafa is funded by Qatar University and QNRF grants. Open Access funding was provided by Qatar National Library.

References

[1] N. Eliyatkin, et al., Molecular classification of breast carcinoma: from traditional, old-fashioned way to a new age, and a new way, J. Breast Health 11 (2) (2015) 59–66.
[2] Y.S. Sun, et al., Risk factors and preventions of breast cancer, Int J. Biol. Sci. 13 (11) (2017) 1387–1397.
[3] A.O. Eketunde, Diabetes as a risk factor for breast cancer, Cureus 12 (5) (2020), e8010.
[4] P. Ferroni, et al., Type 2 diabetes and breast cancer: the interplay between impaired glucose metabolism and oxidant stress, Oxid. Med Cell Longev. 2015 (2015), 183928.
[5] K.B. Michels, et al., Type 2 diabetes and subsequent incidence of breast cancer in the Nurses' Health Study, Diabetes Care 26 (6) (2003) 1752–1758.
[6] P.J. Hardefeldt, S. Edirimanne, G.D. Eslick, Diabetes increases the risk of breast cancer: a meta-analysis, Endocr. Relat. Cancer 19 (6) (2012) 793–803.
[7] K.S. Peairs, et al., Diabetes mellitus and breast cancer outcomes: a systematic review and meta-analysis, J. Clin. Oncol. 29 (1) (2011) 40–46.
[8] F. Xue, K.B. Michels, Diabetes, metabolic syndrome, and breast cancer: a review of the current evidence, Am. J. Clin. Nutr. 86 (3) (2007) s823–s835.
[9] P.F. Christopoulos, P. Msaouel, M. Koutsilieris, The role of the insulin-like growth factor-1 system in breast cancer, Mol. Cancer 14 (2015) 43.
[10] I.A. Durrani, A. Bhatti, P. John, The prognostic outcome of 'type 2 diabetes mellitus and breast cancer' association pivots on hypoxia-hyperglycemia axis, Cancer Cell Int. 21 (1) (2021) 351.
[11] D.J. Slamon, et al., Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene, Science 235 (4785) (1987) 177–182.
[12] B. Chen, et al., Heterogeneity of genomic profile in patients with HER2-positive breast cancer, Endocr. Relat. Cancer 27 (3) (2020) 153–162.
[13] O. Martinez-Saez, A. Prat, Current and future management of HER2-positive metastatic breast cancer, JCO Oncol. Pract. 17 (10) (2021) 594–604.
[14] F. Ligorio, et al., Hormone receptor status influences the impact of body mass index and hyperglycemia on the risk of tumor relapse in early-stage HER2-positive breast cancer patients, Ther. Adv. Med Oncol. 13 (2021), p. 17588359211006960.
[15] M. Okumura, et al., Leptin and high glucose stimulate cell proliferation in MCF-7 human breast cancer cells: reciprocal involvement of PKC-alpha and PPAR expression, Biochim. Biophys. Acta 1592 (2) (2002) 107–116.
[16] A. Lee, et al., Diabetes as a prognostic factor in HER-2 positive breast cancer patients treated with targeted therapy, Breast Cancer 26 (5) (2019) 672–680.
[17] B. Viollet, et al., Cellular and molecular mechanisms of metformin: an overview, Clin. Sci. 122 (6) (2012) 253–270.
[18] S.I. Al-Juboori, et al., PYK2 promotes HER2-positive breast cancer invasion, J. Exp. Clin. Cancer Res 38 (1) (2019) 210.
[19] Z. Dahmani, et al., Metformin partially reverses the inhibitory effect of co-culture with ER-/PR-/HER2+ breast cancer cells on biomarkers of monocyte antitumor activity, PLoS One 15 (10) (2020), e0240982.
[20] P.C. Chou, et al., Impact of diabetes on promoting the growth of breast cancer, Cancer Commun. 41 (5) (2021) 414–431.
[21] X. He, et al., Metformin and thiazolidinediones are associated with improved breast cancer-specific survival of diabetic women with HER2+ breast cancer, Ann. Oncol. 23 (7) (2012) 1771–1780.
[22] A. Rocca, et al., Phase II study of liposomal doxorubicin, docetaxel and trastuzumab in combination with metformin as neoadjuvant therapy for HER2-positive breast cancer, Ther. Adv. Med Oncol. 13 (2021), p. 1758835920985632.
[23] B. Martin-Castillo, et al., A phase 2 trial of neoadjuvant metformin in combination with trastuzumab and chemotherapy in women with early HER2-positive breast cancer: the METTEN study, Oncotarget 9 (86) (2018) 35687–35704.
[24] E. Cuyas, et al., The C Allele of ATM rs11212617 associates with higher pathological complete remission rate in breast cancer patients treated with neoadjuvant metformin, Front Oncol. 9 (2019) 193.
[25] A. Sonnenblick, et al., Impact of diabetes, insulin, and metformin use on the outcome of patients with human epidermal growth factor receptor 2-positive primary breast cancer: analysis from the ALTTO phase III randomized trial, J. Clin. Oncol. 35 (13) (2017) 1421–1429.
[26] P. Saeedi, et al., Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9(th) edition, Diabetes Res Clin. Pract. 157 (2019), 107843.
[27] Cancer Fact Sheets. 2022, World Health Organization.
[28] A. Satija, et al., Type 2 diabetes and risk of cancer, BMJ Br. Med. J. 350 (2015) g7707.
[29] F. Turati, et al., Diabetes risk reduction diet and the risk of breast cancer, Eur. J. Cancer Prev. 31 (4) (2022) 339–345.
[30] S. Ebrahimi Mousavi, et al., Consumption of "Diabetes Risk Reduction Diet" and odds of breast cancer among women in a middle eastern country, Front Nutr. 9 (2022), 744500.
[31] F.M. Hossain, et al., Association of obesity and diabetes with the incidence of breast cancer in Louisiana, Am. J. Prev. Med 63 (1 Suppl 1) (2022). S83-s92.
[32] P. Ramteke, et al., Hyperglycemia associated metabolic and molecular alterations in cancer risk, progression, treatment, and mortality, Cancers 11 (9) (2019).
[33] K.K. Collins, The diabetes-cancer link, Diabetes Spectr. 27 (4) (2014) 276–280.
[34] A.J. Price, et al., Insulin-like growth factor-I concentration and risk of prostate cancer: Results from the European prospective investigation into cancer and nutrition, Cancer Epidemiol. Biomark. Prev. 21 (9) (2012) 1531–1541.
[35] C. Lao, et al., Association of diabetes and breast cancer characteristics at diagnosis, Cancer Causes Control (2022).

[36] X. Wang, S. Ding, The biological and pharmacological connections between diabetes and various types of cancer, Pathol. Res Pr. 227 (2021), 153641.
[37] H.J. Thompson, et al., Effect of low or high glycemic load diets on experimentally induced mammary carcinogenesis in rats, Mol. Nutr. Food Res 60 (6) (2016) 1416–1426.
[38] S. Bose, C. Zhang, A. Le, Glucose metabolism in cancer: the warburg effect and beyond, Adv. Exp. Med. Biol. 1311 (2021) 3–15.
[39] E. Llop, et al., Glycoprotein biomarkers for the detection of pancreatic ductal adenocarcinoma, World J. Gastroenterol. 24 (24) (2018) 2537–2554.
[40] Roser, M. , H. Ritchie, *Cancer*. Our World in Data, 2015.
[41] IDF Diabetes Atlas 2021 10th edition. 2021, International Diabetes Federation: Brussels, Belgium.
[42] H.I. Kim, H. Lim, A. Moon, Sex differences in cancer: epidemiology, genetics and therapy, Biomol. Ther. 26 (4) (2018) 335–342.
[43] B. Lauby-Secretan, et al., Body fatness and cancer — viewpoint of the IARC working group, New Engl. J. Med. 375 (8) (2016) 794–798.
[44] A. Schienkiewitz, et al., Body mass index history and risk of type 2 diabetes: results from the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study, Am. J. Clin. Nutr. 84 (2) (2006) 427–433.
[45] M.A. Abdul-Ghani, et al., High frequency of pre-diabetes, undiagnosed diabetes and metabolic syndrome among overweight Arabs in Israel, Isr. Med Assoc. J. 7 (3) (2005) 143–147.
[46] P.-S. Jonathan, et al., Worldwide burden of cancer attributable to diabetes and high body-mass index: a comparative risk assessment, Lancet Diabetes Endocrinol. 6 (6) (2018) e6–e15.
[47] A. Jemal, et al., The Cancer Atlas, American Cancer Society, Atlanta, Georgia, 2019.
[48] C.G. Foy, et al., Smoking and incidence of diabetes among U.S. adults: findings from the Insulin Resistance Atherosclerosis Study, Diabetes Care 28 (10) (2005) 2501–2507.
[49] C. Willi, et al., Active smoking and the risk of type 2 diabetes: a systematic review and meta-analysis, JAMA 298 (22) (2007) 2654–2664.
[50] CDC. Diabetes and Prediabetes. 2022; Available from: ⟨https://www.cdc.gov/chronicdisease/resources/publications/factsheets/diabetes-prediabetes.htm⟩.
[51] A.A. Howard, J.H. Arnsten, M.N. Gourevitch, Effect of alcohol consumption on diabetes mellitus: a systematic review, Ann. Intern. Med. 140 (3) (2004) 211–219.
[52] D.O. Baliunas, et al., Alcohol as a risk factor for type 2 diabetes: a systematic review and meta-analysis, Diabetes Care 32 (11) (2009) 2123–2132.
[53] J. Li, et al., Liver enzymes, alcohol consumption and the risk of diabetes: the Suita study, Acta Diabetol. 59 (12) (2022) 1531–1537.
[54] S.-W. Chen, et al., Use of thiazolidinediones and the risk of colorectal cancer in patients with diabetes: a nationwide, population-based, case-control study, Diabetes Care 36 (2) (2013) 369–375.
[55] T. Okumura, Mechanisms by which thiazolidinediones induce anti-cancer effects in cancers in digestive organs, J. Gastroenterol. 45 (11) (2010) 1097–1102.
[56] H.C. Lin, et al., Dose effect of thiazolidinedione on cancer risk in type 2 diabetes mellitus patients: a six-year population-based cohort study, J. Clin. Pharm. Ther. 39 (4) (2014) 354–360.
[57] M. Monami, I. Dicembrini, E. Mannucci, Thiazolidinediones and cancer: results of a meta-analysis of randomized clinical trials, Acta Diabetol. 51 (1) (2014) 91–101.
[58] R. Du, et al., Thiazolidinedione therapy and breast cancer risk in diabetic women: a systematic review and meta-analysis, Diabetes Metab. Res. Rev. 34 (2) (2018).
[59] L. Sciacca, R. Le Moli, R. Vigneri, Insulin analogs and cancer, Front. Endocrinol. (2012) **3**.
[60] L. Wu, et al., Decoupling feedforward and feedback structures in hybrid active noise control systems for uncorrelated narrowband disturbances, J. Sound Vib. 350 (2015) 1–10.
[61] R.E. Farmer, et al., Metformin and cancer in type 2 diabetes: a systematic review and comprehensive bias evaluation, Int J. Epidemiol. 46 (2) (2017) 728–744.
[62] T. Yang, Y. Yang, S. Liu, Association between metformin therapy and breast cancer incidence and mortality: evidence from a meta-analysis, J. Breast Cancer 18 (3) (2015) 264–270.
[63] G.H. Tang, et al., Association of Metformin with Breast Cancer Incidence and Mortality in Patients with Type II diabetes: a GRADE-assessed systematic review and meta-analysis, Cancer Epidemiol. Biomark. Prev. 27 (6) (2018) 627–635.
[64] K. Zhang, et al., Metformin and risk of cancer among patients with type 2 diabetes mellitus: A systematic review and meta-analysis, Prim. Care Diabetes 15 (1) (2021) 52–58.
[65] N.F. Col, et al., Metformin and breast cancer risk: a meta-analysis and critical literature review, Breast Cancer Res. Treat. 135 (3) (2012) 639–646.
[66] G. Rennert, et al., Use of metformin and risk of breast and colorectal cancer, Diabetes Res Clin. Pract. 165 (2020), 108232.
[67] H.J. Seo, H.S. Oh, Effects of early medication treatment and metformin use for cancer prevention in diabetes patients: a nationwide sample cohort study in Korea using extended landmark time analysis, Epidemiol. Health 43 (2021), e2021103.
[68] J.L. Feng, X. Qin, Metformin and cancer-specific survival among breast, colorectal, or endometrial cancer patients: A nationwide data linkage study, Diabetes Res. Clin. Pract. 175 (2021), 108755.
[69] S. Zhong, et al., Metformin use and survival of lung cancer patients: Meta-analysis findings, Indian J. Cancer 54 (1) (2017) 63–67.
[70] S.J. Ma, et al., Metformin use improves survival of diabetic liver cancer patients: systematic review and meta-analysis, Oncotarget 7 (40) (2016) 66202–66211.
[71] C. Coyle, et al., Metformin as an adjuvant treatment for cancer: a systematic review and meta-analysis, Ann. Oncol. 27 (12) (2016) 2184–2195.
[72] Q. Wang, et al., Metformin and survival of women with breast cancer: A meta-analysis of randomized controlled trials, J. Clin. Pharm. Ther. 47 (3) (2022) 263–269.
[73] K. Tądel, et al., Metformin and proliferation of cancer cell lines, Pediatr. Endocrinol. Diabetes Metab. 26 (4) (2020) 159–166.
[74] L. Yao, et al., Metformin use and lung cancer risk in diabetic patients: a systematic review and meta-analysis, Dis. Markers (2019) **2019**.
[75] J. Kang, et al., The associations of aspirin, statins, and metformin with lung cancer risk and related mortality: a time-dependent analysis of population-based nationally representative data, J. Thorac. Oncol. 16 (1) (2021) 76–88.
[76] J.J. Sung, et al., Use of metformin and aspirin is associated with delayed cancer incidence, Cancer Epidemiol. 69 (2020), 101808.
[77] L. Durai, et al., Synergistic effect of metformin and vemurafenib (PLX4032) as a molecular targeted therapy in anaplastic thyroid cancer: an in vitro study, Mol. Biol. Rep. 48 (11) (2021) 7443–7456.
[78] N. Ozdemir Kutbay, et al., Effects of metformin and pioglitazone combination on apoptosis and AMPK/mTOR signaling pathway in human anaplastic thyroid cancer cells, J. Biochem. Mol. Toxicol. 34 (10) (2020), e22547.
[79] M. Zhao, et al., Aspirin and metformin exhibit antitumor activity in murine breast cancer, Oncol. Rep. 39 (3) (2018) 1414–1422.
[80] M. Xin, et al., Formononetin and metformin act synergistically to inhibit growth of MCF-7 breast cancer cells in vitro, Biomed. Pharm. 109 (2019) 2084–2089.
[81] X. Zhang, et al., AMPK phosphorylates and stabilises copper transporter 1 to synergise metformin and copper chelator for breast cancer therapy, Br. J. Cancer (2023).
[82] J. Faria, et al., Metformin and breast cancer: molecular targets, J. Mammary Gland Biol. Neoplasia 24 (2) (2019) 111–123.
[83] J. Klubo-Gwiezdzinska, et al., Treatment with metformin is associated with higher remission rate in diabetic patients with thyroid cancer, J. Clin. Endocrinol. Metab. 98 (8) (2013) 3269–3279.
[84] E.J. Gallagher, D. LeRoith, The proliferating role of insulin and insulin-like growth factors in cancer, Trends Endocrinol. Metab. 21 (10) (2010) 610–618.
[85] X. Dai, et al., AMPK-dependent phosphorylation of the GATOR2 component WDR24 suppresses glucose-mediated mTORC1 activation, Nat. Metab. 5 (2) (2023) 265–276.
[86] W.W. Wheaton, et al., Metformin inhibits mitochondrial complex I of cancer cells to reduce tumorigenesis, Elife 3 (2014), e02242.
[87] I.S. Song, J. Han, H.K. Lee, Metformin as an anticancer drug: A Commentary on the metabolic determinants of cancer cell sensitivity to glucose limitation and biguanides, J. Diabetes Investig. 6 (5) (2015) 516–518.
[88] X. Zhou, et al., Metformin inhibit lung cancer cell growth and invasion in vitro as well as tumor formation in vivo partially by activating PP2A, Med Sci. Monit. 25 (2019) 836–846.
[89] G. Yenmiş, et al., Metformin promotes apoptosis in primary breast cancer cells by downregulation of cyclin D1 and upregulation of P53 through an AMPK-alpha independent mechanism, Turk. J. Med. Sci. 51 (2) (2021) 826–834.
[90] G. Yenmis, et al., Anti-cancer effect of metformin on the metastasis and invasion of primary breast cancer cells through mediating NF-kB activity, Acta Histochem. 123 (4) (2021), 151709.
[91] J. Liu, et al., Metformin suppresses proliferation and invasion of drug-resistant breast cancer cells by activation of the Hippo pathway, J. Cell Mol. Med. 24 (10) (2020) 5786–5796.
[92] E. Strekalova, et al., Metformin sensitizes triple-negative breast cancer to proapoptotic TRAIL receptor agonists by suppressing XIAP expression, Breast Cancer Res. Treat. 163 (3) (2017) 435–447.
[93] S. Liu, et al., Upregulation of endogenous TRAIL-elicited apoptosis is essential for metformin-mediated antitumor activity against TNBC and NSCLC, Mol. Ther. Oncol. 21 (2021) 303–314.
[94] M. Daugan, et al., Metformin: An anti-diabetic drug to fight cancer, Pharmacol. Res. 113 (2016) 675–685.
[95] R. Wang, et al., Metformin inducing the change of functional and exhausted phenotypic tumor-infiltrated lymphocytes and the correlation with jnk signal pathway in triple-negative breast cancer, Breast Cancer 14 (2022) 391–403.
[96] R.S. Wahdan-Alaswad, et al., Metformin targets glucose metabolism in triple negative breast cancer, J. Oncol. Transl. Res 4 (1) (2018).
[97] M. Cejuela, et al., Metformin and breast cancer: Where are we now? Int J. Mol. Sci. 23 (5) (2022).
[98] R.A. Hampsch, et al., AMPK activation by metformin promotes survival of dormant ER(+) breast cancer cells, Clin. Cancer Res 26 (14) (2020) 3707–3719.
[99] A. Farahi, et al., Crocin and Metformin suppress metastatic breast cancer progression via VEGF and MMP9 downregulations: in vitro and in vivo studies, Mol. Cell Biochem. 476 (9) (2021) 3341–3351.
[100] P.M.M. Lusica, et al., A systematic review and meta-analysis on the efficacy and safety of metformin as adjunctive therapy among women with metastatic breast cancer, Cancer Treat. Res. Commun. 29 (2021), 100457.
[101] B.H. Kim, M.J. Cho, J. Kwon, Potential intrinsic subtype dependence on the association between metformin use and survival in surgically resected breast cancer: a Korean national population-based study, Int. J. Clin. Oncol. 26 (11) (2021) 2004–2016.
[102] A.C. Cooper, et al., Changes in [18F]Fluoro-2-deoxy-d-glucose incorporation induced by doxorubicin and anti-HER antibodies by breast cancer cells modulated by co-treatment with metformin and its effects on intracellular signalling, J. Cancer Res. Clin. Oncol. 141 (9) (2015) 1523–1532.
[103] J. Ma, et al., Metformin enhances tamoxifen-mediated tumor growth inhibition in ER-positive breast carcinoma, BMC Cancer 14 (2014) 172.

[104] Y. Xiao, et al., Co-delivery of metformin and paclitaxel via folate-modified pH-sensitive micelles for enhanced anti-tumor efficacy, AAPS PharmSciTech 19 (5) (2018) 2395–2406.
[105] G. Ariaans, et al., Anti-tumor effects of everolimus and metformin are complementary and glucose-dependent in breast cancer cells, BMC Cancer 17 (1) (2017).
[106] L.S. Guo, et al., Synergistic antitumor activity of vitamin D3 combined with metformin in human breast carcinoma MDA-MB-231 cells involves m-TOR related signaling pathways, Pharmazie 70 (2) (2015) 117–122.
[107] R.R. Falah, W.H. Talib, S.J. Shbailat, Combination of metformin and curcumin targets breast cancer in mice by angiogenesis inhibition, immune system modulation and induction of p53 independent apoptosis, Ther. Adv. Med. Oncol. 9 (4) (2017) 235–252.
[108] P.J. Goodwin, et al., Effect of metformin vs placebo on invasive disease-free survival in patients with breast cancer: the MA.32 randomized clinical trial, Jama 327 (20) (2022) 1963–1973.
[109] M. Rao, et al., Effects of metformin treatment on radiotherapy efficacy in patients with cancer and diabetes: a systematic review and meta-analysis, Cancer Manag Res. 10 (2018) 4881–4890.
[110] J.O. Lee, et al., Metformin overcomes resistance to cisplatin in triple-negative breast cancer (TNBC) cells by targeting RAD51, Breast Cancer Res. 21 (1) (2019) 115.
[111] T. Cheng, et al., Metformin inhibits the tumor-promoting effect of low-dose resveratrol, and enhances the anti-tumor activity of high-dose resveratrol by increasing its reducibility in triple negative breast cancer, Free Radic. Biol. Med. 180 (2022) 108–120.
[112] C. Christodoulou, et al., Evaluation of the Insulin-like Growth Factor Receptor Pathway in Patients with Advanced Breast Cancer Treated with Trastuzumab, Cancer Genom. Proteom. 15 (6) (2018) 461–471.
[113] J.M. Carboni, et al., Tumor development by transgenic expression of a constitutively active insulin-like growth factor I receptor, Cancer Res 65 (9) (2005) 3781–3787.
[114] S.E. Dunn, et al., A dominant negative mutant of the insulin-like growth factor-I receptor inhibits the adhesion, invasion, and metastasis of breast cancer, Cancer Res. 58 (15) (1998) 3353–3361.
[115] Y. Tao, et al., Mechanisms of disease: signaling of the insulin-like growth factor 1 receptor pathway–therapeutic perspectives in cancer, Nat. Clin. Pract. Oncol. 4 (10) (2007) 591–602.
[116] J.S. Lee, C.E. Tocheny, L.M. Shaw, The insulin-like growth factor signaling pathway in breast cancer: an elusive therapeutic target, Life 12 (12) (2022).
[117] H. Werner, D. LeRoith, Hallmarks of cancer: The insulin-like growth factors perspective, Front Oncol. 12 (2022), 1055589.
[118] H. Li, et al., IGF-IR signaling in epithelial to mesenchymal transition and targeting IGF-IR therapy: overview and new insights, Mol. Cancer 16 (1) (2017) 6.
[119] Y. Lu, et al., Insulin-like growth factor-I receptor signaling and resistance to trastuzumab (Herceptin), J. Natl. Cancer Inst. 93 (24) (2001) 1852–1857.
[120] E. Sanabria-Figueroa, et al., Insulin-like growth factor-1 receptor signaling increases the invasive potential of human epidermal growth factor receptor 2-overexpressing breast cancer cells via Src-focal adhesion kinase and forkhead box protein M1, Mol. Pharmacol. 87 (2) (2015) 150–161.
[121] Q. Jin, F.J. Esteva, Cross-talk between the ErbB/HER family and the type I insulin-like growth factor receptor signaling pathway in breast cancer, J. Mammary Gland Biol. Neoplasia 13 (4) (2008) 485–498.
[122] D. Gajria, S. Chandarlapaty, HER2-amplified breast cancer: mechanisms of trastuzumab resistance and novel targeted therapies, Expert Rev. Anticancer Ther. 11 (2) (2011) 263–275.
[123] N.E. Hynes, H.A. Lane, ERBB receptors and cancer: the complexity of targeted inhibitors, Nat. Rev. Cancer 5 (5) (2005) 341–354.
[124] R. Nahta, et al., Insulin-like growth factor-I receptor/human epidermal growth factor receptor 2 heterodimerization contributes to trastuzumab resistance of breast cancer cells, Cancer Res. 65 (23) (2005) 11118–11128.
[125] A. Camirand, Y. Lu, M. Pollak, Co-targeting HER2/ErbB2 and insulin-like growth factor-1 receptors causes synergistic inhibition of growth in HER2-overexpressing breast cancer cells, Med. Sci. Monit. 8 (12) (2002) Br521–Br526.
[126] H.X. Chen, E. Sharon, IGF-1R as an anti-cancer target–trials and tribulations, Chin. J. Cancer 32 (5) (2013) 242–252.
[127] S. Manda, et al., Design, synthesis, and biological evaluation of proteolysis targeting chimeras (PROTACs) for the dual degradation of IGF-1R and Src, Molecules 25 (8) (2020).
[128] J. van der Veeken, et al., Crosstalk between epidermal growth factor receptor- and insulin-like growth factor-1 receptor signaling: implications for cancer therapy, Curr. Cancer Drug Targets 9 (6) (2009) 748–760.
[129] Y. Ma, et al., InsR/IGF1R pathway mediates resistance to EGFR inhibitors in glioblastoma, Clin. Cancer Res. 22 (7) (2016) 1767–1776.
[130] I. Singh, et al., Targeting EGFR and IGF 1R: a promising combination therapy for metastatic cancer, Front Biosci. 5 (1) (2013) 231–246.
[131] T. Yamaoka, et al., Distinct afatinib resistance mechanisms identified in lung adenocarcinoma harboring an EGFR mutation, Mol. Cancer Res 15 (7) (2017) 915–928.
[132] C. Liu, et al., Crosstalk between IGF-1R and other tumor promoting pathways, Curr. Pharm. Des. 20 (17) (2014) 2912–2921.
[133] T.W. Chen, et al., Metformin inhibits proliferation and promotes apoptosis of HER2 positive breast cancer cells by downregulating HSP90, J. Buon 18 (1) (2013) 51–56.
[134] J. Wang, et al., Suppression of tumor angiogenesis by metformin treatment via a mechanism linked to targeting of HER2/HIF-1α/VEGF secretion axis, Oncotarget 6 (42) (2015) 44579–44592.
[135] I.N. Alimova, et al., Metformin inhibits breast cancer cell growth, colony formation and induces cell cycle arrest in vitro, Cell Cycle 8 (6) (2009) 909–915.
[136] A. Vazquez-Martin, C. Oliveras-Ferraros, J.A. Menendez, The antidiabetic drug metformin suppresses HER2 (erbB-2) oncoprotein overexpression via inhibition of the mTOR effector p70S6K1 in human breast carcinoma cells, Cell Cycle 8 (1) (2009) 88–96.
[137] A. Vazquez-Martin, et al., The anti-diabetic drug metformin suppresses self-renewal and proliferation of trastuzumab-resistant tumor-initiating breast cancer stem cells, Breast Cancer Res Treat. 126 (2) (2011) 355–364.
[138] S. Orecchioni, et al., The biguanides metformin and phenformin inhibit angiogenesis, local and metastatic growth of breast cancer by targeting both neoplastic and microenvironment cells, Int J. Cancer 136 (6) (2015) E534–E544.
[139] V.N. Anisimov, et al., Effect of metformin on life span and on the development of spontaneous mammary tumors in HER-2/neu transgenic mice, Exp. Gerontol. 40 (8–9) (2005) 685–693.
[140] V.N. Anisimov, et al., Metformin decelerates aging and development of mammary tumors in HER-2/neu transgenic mice, Bull. Exp. Biol. Med 139 (6) (2005) 721–723.
[141] I.G. Popovich, et al., Insulin in aging and cancer: antidiabetic drug Diabenol as geroprotector and anticarcinogen, Int J. Biochem Cell Biol. 37 (5) (2005) 1117–1129.
[142] A. Vazquez-Martin, et al., The antidiabetic drug metformin: a pharmaceutical AMPK activator to overcome breast cancer resistance to HER2 inhibitors while decreasing risk of cardiomyopathy, Ann. Oncol. 20 (3) (2009) 592–595.
[143] G. Jerusalem, P. Lancellotti, S.B. Kim, HER2+ breast cancer treatment and cardiotoxicity: monitoring and management, Breast Cancer Res Treat. 177 (2) (2019) 237–250.
[144] M. Jalving, et al., Metformin: taking away the candy for cancer? Eur. J. Cancer 46 (13) (2010) 2369–2380.
[145] R.T. Chlebowski, et al., Diabetes, metformin, and breast cancer in postmenopausal women, J. Clin. Oncol. 30 (23) (2012) 2844–2852.
[146] G. Hou, et al., Clinical pathological characteristics and prognostic analysis of 1,013 breast cancer patients with diabetes, Breast Cancer Res Treat. 137 (3) (2013) 807–816.
[147] W. Min, et al., The effect of metformin on the clinicopathological features of breast cancer with type 2 diabetes, World J. Oncol. 11 (1) (2020) 23–32.
[148] B. Martin-Castillo, et al., A phase 2 trial of neoadjuvant metformin in combination with trastuzumab and chemotherapy in women with early HER2-positive breast cancer: the METTEN study, Oncotarget 9 (86) (2018) 35687–35704.
[149] K. Zhou, et al., Common variants near ATM are associated with glycemic response to metformin in type 2 diabetes, Nat. Genet 43 (2) (2011) 117–120.
[150] E. Cuyàs, B. Martin-Castillo, J.A. Menendez, Metformin and breast cancer: an opportunity for pharmacogenetics, Aging (Albany NY) 14 (14) (2022) 5612–5613.
[151] H. Chen, et al., Relationship between diabetes and diabetes medications and risk of different molecular subtypes of breast cancer, Cancer Epidemiol. Biomark. Prev. 28 (11) (2019) 1802–1808.