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In silico and *in vitro* assessment of anti-proliferative and pro-apoptotic potential of quercetin derivatives on Luminal A breast cancer cells

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ABSTRACT

Anti-hormone therapy is a conventional and established remedy to treat Luminal A breast cancer. Howbeit, about 20–30% of tumors are resistant to hormone therapy. Phytotherapeutic agents have evinced prophylactic and therapeutic capacities in breast carcinomas. Tamarixetin, a natural O-methylated flavonol, exhibited anti-inflammatory, cardiotonic, gastroprotective properties and mediated the suppression multidrug resistance proteins. However, effects of tamarixetin on Luminal A breast cancer are underexplored compared to quercetin. This survey compares the molecular docking of tamarixetin and quercitrin to apoptosis-related proteins. Based on which, the cytotoxicity and apoptosis induction potency of the more favorable flavonoids on MCF-7 cancer cells were assessed. The results displayed relatively higher negative binding energy, and consequently more effective interactions of tamarixetin with p21, p53, Bax, Bcl2 and caspase 8 in comparison to quercitrin. It was found that treatment of MCF-7 cells with tamarixetin engenders a decrease in viability in a time and dose-dependent manner. Tamarixetin-induced apoptosis in MCF-7 cells was evidenced via flowcytometry. Gene expression analysis affirmed that tamarixetin exerted pro-apoptotic potential through activation of the extrinsic pathway of apoptosis via activation of caspase 8, and the intrinsic pathway of apoptosis by stimulation of p53 and its essential downstream target, p21. This flavonol enhanced the expression of anti-oxidant enzymes (SOD1 and SOD2) independently, or dependent on p53. Our outcomes propose tamarixetin as an auspicious complementary anti-cancer herbal candidate for therapy of Luminal A breast cancer, worthy of further investigation.

Keywords: Tamarixetin, Quercitrin, Luminal A breast cancer, Anti-proliferation, Proapoptotic.

INTRODUCTION

Breast carcinoma has been recognized as the most prevalent malignancy and second leading cause of cancer mortality in women worldwide [1, 2]. Progress in molecular biology has prompted the classification of mammary cancers based on tumor endocrine responsiveness. Accordingly, breast cancer has been assigned to four molecular subtests: Luminal A (ER+/PR+/HER2-/lowKi-67), Luminal B (ER+/PR+/HER2-/+/high Ki-67),

HER2-overexpression (ER-/PR-/HER2+) and triple negative breast cancers (TNBCs) (ER-/PR-/HER2-) [3]. The luminal (Hormone Receptor-Positive) subtype constitutes about two thirds of all breast cancers. Luminal breast cancer displays extreme heterogeneity, including variations in histology, gene-expression profile, mutations and responses to treatment [4]. The conventional treatment for luminal breast cancer patients is endocrine therapy, mainly with tamoxifen [5]. Luminal A, the more frequent subtype, is considered to have higher responsiveness to endocrine treatment than luminal B [6]. While endocrine therapy has attained admissible outcomes, around 20–30% of tumors are resistant to endocrine remedies [7, 8]. These malignancies are either inherently resistant to endocrine therapy or acquire resistance subsequent to long-term exposure to hormones [9].

A growing volume of research has evidenced the prophylactic and therapeutic effects of natural products on breast malignancies, through their antioxidant, anti-inflammatory and immunomodulatory potentials, and their ability to induce apoptosis and suppress proliferation of cancer cells [10] by Phytotherapeutic agents exhibiting minimal adverse effects, low toxicity and less recurrent resistance to hormonal anti-cancer drugs [11]. In the vast territory of herbal compounds, flavonoids represent a broad group of plant secondary metabolites, as a family of polyphenols with a basic benzo-γ-pyrone structure naturally occurring in many fruits, vegetables, and herbs [12, 13]. Flavonoids have received ample consideration thanks to their extensive spectrum of salubrious features, including nutraceutical, pharmaceutical and cosmeceutical benefits [14], and pharmacological properties such as antioxidant, antibacterial, anti-inflammatory, anti-allergic and anti-cancer potentials [15-19]. Flavonoids illustrated anti-breast cancer activities through repression of cell proliferation and induction of cell cycle arrest, DNA damage, apoptosis, autophagy, and improved anti-tumor immunity [20-25]. Tamarixetin (Fig.1a), 3,5,7,3′-tetrahydroxy-4′-methoxy flavonol - essentially isolated from the leaves of *Azadirachta Indica* L. (neem), *Tamarix Ramosissima* L. (salt cedar) and *Psidium Guajava* L. (guava) - is a natural O-methylated flavonol metabolized from quercetin (3, 3′, 4′, 5, 7-pentahydroxy flavanone) as a flavanone-type flavonoid which is presented in human diet [26, 27]. Tamarixetin exhibited anti-inflammatory [28], cardioprotective [29], gastroprotective [30] and multidrug resistance protein (MDR) abilities [31]. Quercitrin (Fig.1b) (2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4-oxo-4H-chromen-3-yl 6-deoxy-alpha-L-mannopyranoside) or quercetin-3-*O*-rhamnosid is naturally occurring flavonoids in some fruits and vegetables, such as apples, onions and berries [32, 33]. It has exhibited vigorous antioxidant and anti-inflammatory, anti-neoplastic, cardioprotective, neuroprotective, anti-allergic and anti-viral functionalities [33, 34].

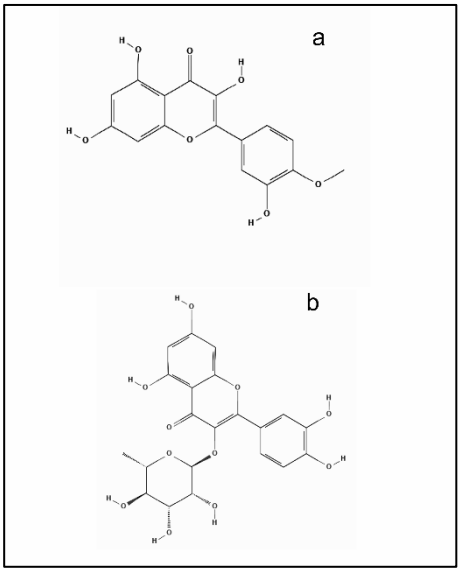

Figure 1. Chemical structure of **A)** Tamarixetin, **B)** Quercitrin (Pubchem).

It has been claimed that quercetin derivatives, such as Tamarixetin and Quercitrin, might vary on functional traits. The particular site of functionalization in quercetin derivatives directly regulates their bioactivity. Despite the myriad of studies suggesting the anti-inflammatory, anti-oxidant, anti-proliferative, anti-angiogenic, pro-apoptotic properties of quercetin on breast cancer [35], assessment of the anti-breast cancer potencies of tamarixetin and quercitrin remains unmet. Therefore, in the present study the molecular docking of tamarixetin/quercitrin to the apoptosis related proteins was studied, and based on the docking scores the cytotoxic and pro-apoptotic features of the more favorable flavonoids on luminal A breast cancer cells were investigated.

MATERIAL AND METHODS

Molecular docking

The 3D chemical structure of the proteins p53, p21, BAX, BCL-2 and Caspase 8 were obtained from the uniprot database (https://www.uniprot.org/) and the structure of the quercetin derivatives (tamarixetin and quercitrin) were obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). The molecular docking was carried out using the PyRx 0.8 software. The proteins were optimized using the ViewerLite 5.0 software. All water molecules and nonpolar hydrogens of the proteins were eliminated, afterwards the ligand was attached. Subsequently, the modified protein structures (in PDB format) and the three-dimensional tamarixetin and quercitrin structure (in SDF format) were imported in the PyRx software, and the proteins' optimal binding sites were independently discovered using deep site (Table 1). The grid box and the coordinates obtained from deep site were input into the Pyrex software, and the docking outcomes were computed.

Table 1. Molecular Docking Parameters and Protein Targets.

Protein	PDB ID	Resolution (Å)	Grid Box Center Coordinates (Å)	Grid Box Size	Conformers Generated per Ligand
P53	1kzy	2.5	center_x= 39.2347 center_y= 30.5802 center_z= 49.742	size_x = 25.0 size_y= 25.0 size_z= 25.0	7
P21	6ahu	3.66	center_x= 139.495 center_y= 168.412 center_z= 187.074	size_x = 40.045 size_y= 40.045 size_z= 40.045	7
BCL2	2xa0	2.70	center_x= 33.8217 center_y= -14.1731 center_z= -14.1785	size_x = 25.0 size_y= 25.0 size_z= 25.0	7
Bax	4bd7	2.80	center_x=75.7590 center_y=71.4811 center_z= 64.1084	size_x = 25.0 size_y= 25.0 size_z= 25.0	7
Caspase8	1f9e	2.90	center_x= 47.685 center_y= 43.487 center_z= 38.356	size_x = 25.0 size_y= 25.0 size_z= 25.0	7

Cell culture

The luminal A human breast carcinoma cells, MCF7, were purchased from the Pasteur Institute (Tehran, Iran). They were cultured in DMEM High Glucose complemented with 10% fetal bovine serum (FBS) and antibiotic (1% penicillin-streptomycin) and incubated in 5% CO_2 atmosphere at 37˚C.

Cell viability assay

The anti-proliferative potency of tamarixetin on the MCF7 cells was evaluated using MTT assay. 5000 cells per well were seeded in 96-well plates overnight. The following day, they were exposed to 0-50µg/ml of tamarixetin for 24 and 48 hours. Subsequently, the medium was discarded and 200µL of 3-(4,5-dimethylthiazol-2-yl)-2,5- diphenyltetrazolium bromide (MTT) solution was added to each well and maintained at 37 °C for 4 hours. Following the removal of the MTT solution, 100µL of dimethyl sulfoxide (DMSO) was added and the plates were put in a shaker incubator for 15min. The absorbance of each well was read using a microplate reader at 570nm.

Apoptosis assay

In order to assess the apoptosis incurred by tamarixetin, Annexin V staining (Annexin-V-FLUOS staining kit (Roche, Germany)) was carried. Following the treatment of the MCF7 with 25µg/ml tamarixetin for 24h, the treated cells were recovered and washed twice with 2mL of ice-cold PBS buffer. Then, the mammary cancer cells were incubated for 15 min with 100µL of HEPES buffer comprising (including) 20µL of FLUOS-conjugated Annexin V and 20µL of PI. The stained cells were rapidly analyzed with a flowcytometer.

Real Time-PCR assay

After pretreatment of MCF7 cells with 25µg/ml of Tamarixetin for 24h, the total RNA was extracted from the cancerous cells by TRIzol® (Invitrogen). The quantity and quality of the isolated RNA was characterized by Nanodrop and agarose gel electrophoresis (1% agarose). The cDNA was synthesized using a Primescript^{TM}RT Reagent Kit (Perfect Realtime) (Takara, China). The primers for genes, P53, P21, Caspase 8, BCL2, superoxide dismutase1 (SOD1*),* superoxide dismutase2 (SOD2), and the housekeeping gene glyceraldehydes 3-phosphate dehydrogenase (GAPDH), were designed via Oligo7 software (Table 2). Quantitative PCR amplification was done with a light cycler instrument (Applied Biosystems7500, USA) using 5x HOT FIREPol®EvaGreen® qPCR Mix Plus (ROX) (Solis BioDyneInc). The achieved threshold cycle (Ct) values were processed for further evaluations, according to the comparative C_t method. The Expression levels of each gene were standardized to the GAPDH, giving the ΔC_t value. The expression level of each mRNA was computed on the basis of the comparative Ct ($2^{-\Delta\Delta Ct}$) method.

Table 2. Nucleotide Sequences of the Primers Used for Real-time RT-PCR

Gene	Sequences (5' to 3')	Annealing temperature (°C)	Fragment length
P53	F: GGTACCGTATGAGCCACCTG R: AACCTCAAAGCTGTCCCGTC	58	166
P21	F: ACTCTCAGGGTCGAAAACGG R: GATGTAGAGCGGGCCTTTGA	60	150
Bcl2	F: TCTTTGAGTTCGGTGGGGTC R: GTTCCACAAAGGCATCCCAG	58	153
Sod1	F: ACAAAGATGGTGTGGCCGAT R: AACGACTTCCAGCGTTTCCT	60	162
Sod2	F: GGTCTGCATTATGCTTGCATGT R: GACTGGAGATACAGGTCTTGGTC	60	141
Caspase 8	F: AGCAGCCTATGCCACCTAGT R: GCTGTAACCTGTCGCCGAG	59	261
GAPDH	F: AAGTTCAACGGCACAGTCAAGG R: CATACTCAGCACCAGCATCACC	58	121

Statistical analysis

All the data are rendered as mean ± SD from at least three independent experiments. The statistical significance of the variation detected between the tamarixetin-treated group and the non-treated group was defined by the student's t-test, and p-values<0.05 were considered significant.

RESULTS AND DISCUSSIONS

In silico prediction of tamarixetin and quercitrin interaction with apoptosis-associated proteins by molecular docking

Drug discovery is a protracted and costly process, with no guarantee of success [36, 37]. Virtual screening via molecular docking develops an alternative approach to screening of millions of compounds from pharmaceutical libraries in a brief period [38]. Molecular docking in herbal-based drug discovery can explicate traditional applications as well as potentially point out novel merits for herbal remedies [39]. Therefore, initially, the molecular docking of tamarixetin/quercitrin with apoptotic proteins was studied and accordingly, tamarixetin exhibiting a higher negative binding energy and greater selectivity towards the apoptosis related proteins, was opted for *in vitro* investigations.

The protein–tamarixetin/quercitrin docking outcomes are displayed in tables 3a and 3b. Tamarixetin revealed higher negative binding energy, and accordingly more efficient interactions with p21, p53, Bax, Bcl2 and caspase 8 in comparison to quercitrin. The binding energy evaluations suggested tumor suppressors p53 and p21, as the main targets for tamarixetin, while p21 was recommended as the essential objective for quercitrin. Some studies consider docking RMSDs between 2 and 3Å as partial successes [40]. Accordingly, caspase 8 shows a more proper RMSD in interaction with tamarixetin and quercitrin, whereas unfavorable values of RMSD were reported for interaction with Bax and Bcl2. Higher RMSD describes conformational flexibility, since the ligand might adopt a varied conformation in solution in comparison with the crystal structure.

Table 3a. Docking Results of Tamarixetin with Its Potent Targets

Tamarixetin	Binding affinity(kcal/mol)	RMSD lower bound	RMSD upper bound
P53	-8.4	2.029	4.367
P21	-8.5	2.478	3.659
Bax	-6.8	2.779	5.688
BCL2	-6.5	3.019	5.877
Caspase 8	-6.2	1.695	3.628

Table 3b. Docking Results of Quercitrin with Its Potent Targets

Quercitrin	Binding affinity(kcal/mol)	RMSD lower bound	RMSD upper bound
P53	-6.4	2.498	3.488
P21	-7.4	4.121	5.321
Bax	-6.2	3.833	6.593
BCL2	-5.7	4.02	5.67
Caspase 8	-5.8	1.26	2.131

Tamarixetin is an O-methylated and quercitrin is an O-glycoilated flavonoids [41, 42]. Preceding *in vitro* studies expressed that glycosylation of the 3-OH group of flavonoids reduces their antioxidant and anticancer potential [43]. This was attributed to the fact that O-glycosylation elevates steric effects and distorts the coplanarity of the glycosylated ring with the rest of the flavonoid structure and reduces the capacity to delocalize electrons - more so than O-methylation [44, 45].

Effects of tamarixetin on viability of MCF-7**cells**

MTT assay rendered that exposure of MCF-7 cells to various concentrations of tamarixetin caused a decline in cell viability in a time- and dose-dependent manner (Fig. 2). Results are rendered as a percent of viable cells compared to control and are illustrated as mean±SD. Significance was set at **p<0.01; ***p<0.00.1. The IC_{50} values were 25 and 20 µg/ml respectively, for 24h and 48h treatments. Shaji et al., surveyed the effect of treatment with 50 and 100µM, (approximately 15.8 and 31.6 µg/ml) of tamarixetin on MCF-7 cell proliferation. They reported that treating with 50µM of this flavonol for 24 h exerted meager cytotoxicity, in contrast to 48 h exposure, that lead to 92.70% suppression of cell proliferation at 50µM tamarixetin [46]. In further research, IC50 dose was evaluated as 17.8±2.4µM for 72h treatment of MCF-7tamarixetin [47]. It should be noted that emerging evidence suggests that tamarixetin possess selective toxicity against malignant cells, with insignificant toxicity against normal cells [46]. It should be mentioned that according to IC50 dose, 25µg/ml of tamarixetin and 24h treatment, was opted for subsequent assays.

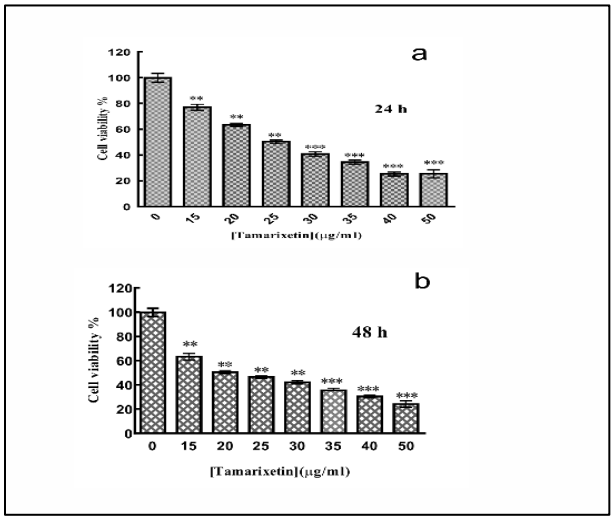

Figure 2. Cytotoxicity of various doses of Tamarixetin (0-50 µg/ml) on MCF-7 cells **A)** treating for 24h. **B)** treating for 48h.

Effects of tamarixetin on induction of apoptosis in MCF-7cells

Subsequent to treating MCF-7 cells with 25µg/ml of tamarixetin for 24h, the apoptosis rate, i.e. the sum of early apoptosis and late apoptosis, were remarkably elevated. As depicted in Fig. 3, around %52 of the cells underwent apoptosis. The early and late apoptosis was induced in respectively %34.17 and %18.23 of breast cancerous cells. An earlier study revealed that tamarixetin promotes the cell cycle arrest at the G2/M phase in MCF-7 cells [46]. Microtubules perform vital roles in the regulation of the mitotic apparatus, as their disorganization generates cell-cycle arrest in the M phase [48]. Several researches confirmed that some flavonoids can disturb tubulin polymerization [49-54]. A study on 79 flavonoid analogues has illustrated the structure-activity relationship with cytotoxicity and interaction with tubulin. The most potent compounds possessed hydroxyl groups at C3' and C5, and also have methoxylated groups at C4' [49]. These structural characteristics are in accordance with tamarixetin, suggesting microtubule disruption and tubulin polymerization as a conceivable underlying mechanism for the cell-cycle effect of tamarixetin.

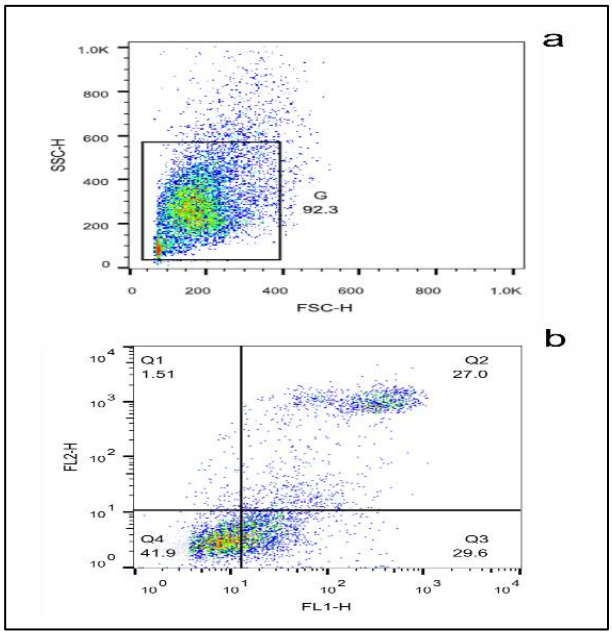

Figure 3. The apoptosis-prompting potentials of Tamarixetin *on* MCF-7 cells assessed by *Annexin* V/PI flow cytometry assay: **A)** control, **B)** 25 µg/ml.

Effects tamarixetin on apoptosis-related gene expression

Real-time polymerase chain reaction was carried out in order to assess the mRNA expression levels of some apoptosis related-genes, subsequent to treatment with 25µg/ml of tamarixetin (Fig. 4). The Data is displayed as the relative expression level compared to *GAPDH* and presented as mean±SD. Significance was set at *p<0.05: **p<0.01; ***p<0.001 Tamarixetin evidently elevated the P53 and P21 mRNA expressions, respectively by 3.52±0.17; p=0.003 and 4.81±0.51; p=0.0004 times, compared to the control (Fig. 4a and b).

The effects of tamarixetinon the expression level of p53 have never been studied before. Howbeit, reports on cervical and gastric cancer cells revealed that amplification of p53 upon quercetin exposure in cells leading to apoptosis [55. 56]. It can be highlighted that Alkhalaf et

al., found that p53 levels seem to command the mechanism(s) whereby hormone therapy exerts anti-proliferative impact on MCF-7 cells [57]. The cytotoxicity of tamarixetin towards leukemic cells via enhancing apoptotic potential is conducted by the increase in p21[47].

Tamarixetin up-regulated the expression of caspase 8 in comparison to the control, 3.44±0.25; p=0.002 folds (Fig. 4c). It downregulated Bcl2 expression considerably. Its expression was attenuated by 5.43±0.01; p=0.0004 folds compared to the control (Fig. 4d). This data is in consonance with a study on HL-60 cells, where activation of caspases-8 was strikingly appreciable after 12 h of tamarixetin therapy and elevated with the incubation time. While, it was declared that Bcl-2 expression remained constant, Bax level (pro-apoptotic) was upregulated. This discord may be ascribed to cell-line-specific responses to tamarixetin. Accordingly, tamarixetin in HL-60 cells triggers apoptosis via Bax overexpression [47]. Furthermore, in a study that depicted the toxicity of quercetin on breast carcinoma cells, quercetin-treated MCF-7 cells remarkably down expressed Bcl-2 in comparison with untreated cells [58].

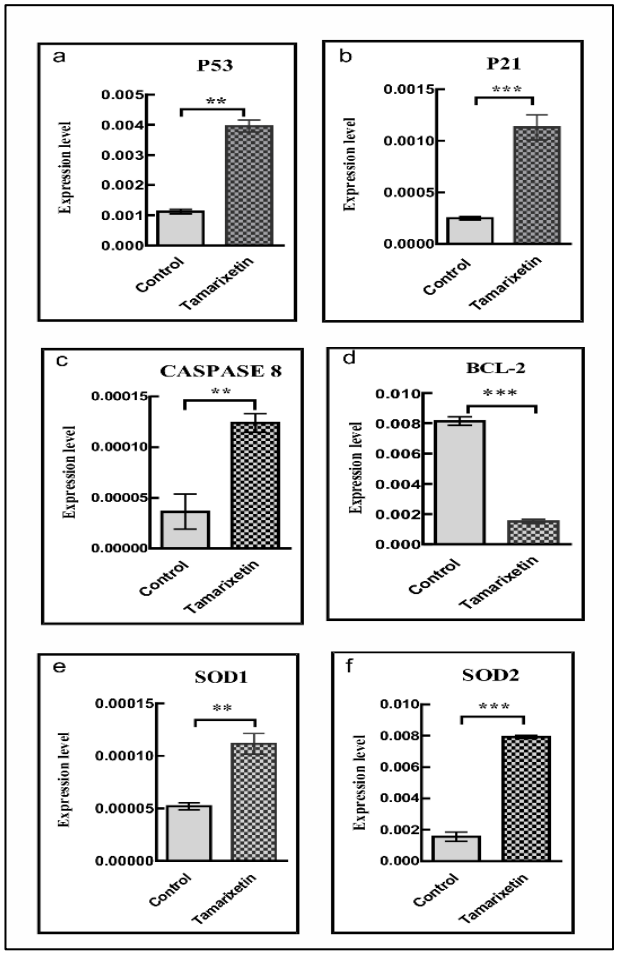

Figure 4. Effect of Tamarixetin on expression Levels of **A)** *P53*, **B)** *P21*, **C)** *caspase 8*, **D)** *BCL 2*, **E)** *SOD1* and **F)** *SOD2* genes, evaluated by Real-time PCR.

Tamarixetin treatment also promoted expression of Sod1 and Sod2 respectively by 2.02±0.17; p=0.002 and 5.06±0.06; p=0.00006 times (Fig. 4e and f). This finding is in accordance with Ijaz et al., since they showed that the activity of SOD was diminished and the level of ROS increased in kidney of rats following cisplatin treatment. While Co-administration of cisplatin+tamarixetin augmented the SOD function, as well as decreased the ROS value, therefore alleviating the renal lesions caused by cisplatin [59]. In 2022 a network analysis through reverse docking identified 539 breast cancer-associated genes, in which 35 genes were found to be the

target of tamarixetin, among them SOD2[46]. Hussain et al., stated that the imbalance of antioxidant enzymes that dictates the production of oxidative stress is connected to p53-mediated apoptosis. It has been illustrated that the elevated level of SOD protein expression is positively associated with the level of p53 induction in TR9-7 cells. Hence, a novel procedure for p53-dependent apoptosis was addressed in which p53-mediated the overexpression of SOD2 [60].

CONCLUSION

In the present survey, molecular docking analysis evinced slightly high negative binding energy and appreciable selectivity between tamarixetin and apoptosis interfering proteins. Our investigation verified the cytotoxicity and apoptotic potencies of tamarixetin on MCF-7 cells. Tamarixetin imposed its effects through induction of the extrinsic pathway of apoptosis via activation of caspase 8 and the intrinsic pathway of apoptosis by stimulation of p53 and it's essential downstream target, p21. Moreover, this flavonoid elevated the expression of anti-oxidant enzymes (SOD1 and SOD2) independently or dependent on p53. The findings of our research propose tamarixetin as an auspicious phytotherapeutic agent for further surveys (e.g., in animal models and combination therapies) for the remedy of Luminal A breast cancer.

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CONFLICT OF INTEREST

The authors should declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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