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ORIGINAL ARTICLE

Aromatase inhibition using Juniperus procera phytochemical constituents: molecular docking study

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Abstract
The key step in the biosynthesis of estrogen is the enzyme activity of aromatase. Several malignancies, including breast cancer, have been linked to the initiation and progression of estrogen overexpression. Exemestane, Arimidex and Femara are the most common aromatase inhibitors used to treat hormone-dependent breast cancers. Drug resistance and side effects are commonly associated with these treatments. The purpose of this in silico study was to list the chemical compounds of *Juniperus procera* that have been published in scientific papers. The second goal was to evaluate the inhibitory activity of 124 phytochemicals of *Juniperus procera* compared to known aromatase inhibitors such as Exemestane, Arimidex and Femara. The 3D structure of aromatase (PDB id: 3s7s) employed for docking studies using AutoDock Tools as well as normal mode analysis studies utilizing the NMSim web server. Juniperolide, Kaurenoic acid and Isocupressic acid were identified as competitive aromatase inhibitors compared to FDA approved anti-cancer drugs, specifically Exemestane, Arimidex and Femara. The stability of the ligand–protein interface was studied to support the docking findings. To our knowledge, this is the first study that investigates the possible inhibition roles of some compounds of *Juniperus procera* on the aromatase enzyme.

Keywords Arar · Anticancer activities · Inhibitors · Phytochemicals · Exemestane · Juniperolide Kaurenoic acid

1 Introduction

The natural diversity in Saudi Arabia, which includes high mountains with heavy rainfall to an extremely parched desert, has resulted in a very diverse and abundant flora. In fact, chemo-diversity between Saudi plants and those cultivated in other nations and climates has been observed to differ significantly in several cases [1]. The *Cupressaceae* family includes the *Juniperus procera* (*J. procera*) plant, whose phytochemicals have been shown to have good antioxidant, antibacterial, and anticancer properties [2]. The plant extracts of *J. procera* and a set of plant-derived compounds with anticancer activities have been identified and separated by several researchers as listed in Table S1. Terpenoids, diterpenes, and essential oils are only a few of the active compounds in this highly valued plant that are responsible for its biological activity [3]. There are many *J. procera* products that have been studied to prove their medicinal benefits. One of the first studies in which *J. procera* products were isolated and their medicinal importance tested was by [4]. In this study, three antimicrobial diterpenoids were produced from the bark of *Juniperus procera*: (+)-E-communication acid, (+)-Z-communication acid, and (+)-Totalol. Totarol, isolated from *J. procera*, showed antimycobacterial properties [5]. In more recent studies, Epicatechin, Podocarpusflavone A and Juniperolide were isolated from the stem bark and leaf of *J. procera* and showed activity against common bean bacterial pathogens [6]. Among the 12 bioactive compounds produced by Gas chromatography–mass spectrometry analysis, the active ingredient 2-imino-6-nitro-2H-1-benzopyran-3-carbothiamide was shown to be the best docked chemical against selected proteins [7].

Plant-based drugs are among the natural products from which 50% of known anti-cancer medications are generated. Most of these compounds are alkaloids, flavonoids, and terpenoids [8]. Terpenes participate in several physiological activities, including growth and development, reproduction, and defense against biotic and abiotic stress. They also play significant roles in the manufacture of secondary metabolites in plants, such as essential oils and pigments [9, 10]. Due to

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their various biological activities, such as their anticancer, anti-inflammatory, antibacterial, and antiviral actions, terpenes are the target of biochemical and molecular research [11]. Terpenes can modulate signaling pathways involved in a variety of cellular activities, including apoptosis, proliferation, and cell differentiation. They can interact with specific biological targets, such as enzymes, receptors, and ion channels [12].

Breast cancer is the most common cancer and the driving cause of cancer-related mortality in women around the world [13]. Its rate is expected to rise strongly within the coming years [14]. Breast cancer is the most common type among women in Saudi Arabia (29%) [15], which requires intensive research among patients to find effective therapies and thus reduce its prevalence. According to the Saudi Cancer Registry, 3954 cases were diagnosed with breast cancer in Saudi women in 2020 [16]. Obesity, young age at menarche, late-age childbirths, short lactation periods, physical inactivity, and environment are a few factors that raise the incidence of breast cancer cases [17]. The current chemotherapy treatments for breast cancer are expensive, associated with several side effects, and may even create resistant cells. This emphasizes the need for natural treatments that can decrease the side effects of utilizing the available chemical treatments [18].

Molecular modelling is a useful method for structure-based drug design. A computer technique known as "docking" makes it possible to predict the shape of the ligand after it binds to a protein target as well as the way that drug-target complexes interact [19]. The era of biological big data is a result of the exponential increase in the amount of biological information produced. It has become more and more important to create computational resources in order to evaluate the molecular characteristics and chemical behaviour of natural products from an in-silico perspective. The analysis and interpretation of these data are currently being done using a variety of bioinformatic techniques, including molecular docking, virtual screening, Quantitative structure–activity relationship (QSAR) and a lot of other computational methods· Das and Agarwal [8] review in detail numerous computational studies that have used plant products as anticancer agents. The future of medical sciences, particularly in the diagnosis and treatment of cancer, appears bright in this era of rapidly advancing technology because of the potential uses of artificial intelligence in clinical operations. The accuracy and precision of artificial intelligence has given scientists and technicians the confidence to extend traditional techniques of research [20].

In vitro and in silico studies have been performed to evaluate the potential impact of many plant-based inhibitors on aromatase [21–23]. Inhibition of the aromatase enzyme has been associated in several studies with the reduction of breast cancer growth [24–26]. The usage of aromatase inhibitors lowers the body's production of estrogen, which in turn slows the growth of breast cancer cells [27]. Aromatase served as a template for ligand-enzyme docking in numerous in silico investigations [21, 28, 29]. For inhibiting aromatase, several synthetic substances have been developed. Additionally, natural compounds are currently used to suppress the aromatase enzyme to find a new breast cancer therapeutic strategy [30]. The current study's objectives were to compile a list of the chemical constituents of *Juniperus procera* that have been reported in academic publications and to investigate any potential inhibition of the aromatase enzyme by phytochemicals found in *J. procera*.

2 Research methods

2.1 Preparation of input files for docking

The Protein Data Bank (PDB) was used to retrieve the crystal structure file of human placental aromatase complexed with the anti-breast cancer medication exemestane (PDB: 3S7S). Exemestane (the native ligand), hetero atoms, and water molecules were removed using Chimaera software tools [31]. 124 phytochemicals from *J. procera* were chosen for docking studies based on a literature review of the substances identified from this plant. These chemicals' 1D structures were found in the PubChem Search database as canonical smiles strings. A web server called CORINA transformed the smiles strings into pdb files [32]. The Chimaera software tools were then used to further prepare each ligand. The ligand preparation includes adding hydrogens, eliminating solvents, and establishing the charge. Three commercially available anti-cancer drugs, Exemestane, Arimidex and Femara were used as controls for the docking.

2.2 Ligand–protein docking

AutoDock Tools (ADT) 1.5.6 optimized the protein molecule (3S7S). As part of the optimization, water molecules are removed, polar hydrogen is added, non-polar hydrogen is combined, and Gasteiger charges are calculated. The grid box had the dimensions 40*40*40 and was centred at x: 86.08, y: 54.28, and z: 46.18. Docking was carried out using the following genetic algorithm parameters: 150 population size, a maximum of 27,000 generations, a mutation rate of 0.02, and a crossover rate of 0.80. Using chimaera software tools and the protein–ligand interaction profiler service [33], conformations with the highest binding affinities were examined following docking. iGEMDOCK 2.1 software [34] was used for a fast primary screening of the 124 J. *procera* phytochemicals, data are shown in Table S1. Three phytochemicals (Table 1) with the highest binding affinity were further investigated and docked using AutoDock tools as mentioned

Table 1 Docking score of *Juniperus procera* phytochemicals, the native inhibitor, and controls against aromatase enzyme

Compound name	Classification	PubChem CID	AutoDock Score	Inhibition Constant nM (nanomolar)
Exemestane	Steroidal drug	60,198	− 12.65	0.53
Arimidex	Non-steroidal drug	2187	− 10.44	22.16
Femara	Non-steroidal drug	3902	− 9.21	178.52
	***J. procera* phytochemicals that gave best binding energy**			
Juniperolide	Terpenes	101,552,747	− 11.33	4.96
Kaurenoic acid	Terpenes	73,062	− 11.20	6.16
Isocupressic acid	Terpenes	6,438,138	− 10.27	29.87

above. The ligand–protein interactions were analyzed using PLIP web server (Protein–Ligand Interaction Profiler) [35].

2.3 Normal mode analysis

Using NMSim web server [36], molecular analysis was carried out to evaluate the conformational changes upon ligands binding in aromatase. The default parameters of NMSim were used. The parameters were as follows: type of simulation was Small Scale Motions, number of trajectories was 1, number of NMSim cycles was 10, step size was 0.5 and the normal mod (NM) range was 1–50. Root-mean-square-deviation (RMSD) was used to show information on the protein's structural changes during the simulation.

2.4 Evaluation of ADMET

Using the SwissADME web server, predictions of ADMET (absorption, distribution, metabolism, excretion, and toxicity) based on Lipinski's rule of five (RO5) were made for all the ligands. Additionally, all the ligands' bioactivity as enzyme inhibitors was determined using the Molinspiration server, available at https://molinspiration.com/cgi-bin/properties. Cytotoxicity was calculated using ProTox-II server [37].

3 Results and discussion

3.1 Validation of docking protocol

To validate the docking protocol of AutoDock software, the native ligand (exemestane) was isolated from the binding site of the aromatase structure (3S7S). AutoDock software was able to redocked the isolated ligand into the binding site of aromatase. The redocked ligand was nearly superimposed with the relevant co-crystallised exemestane indicating the accuracy of docking protocol as shown in Fig. 1.

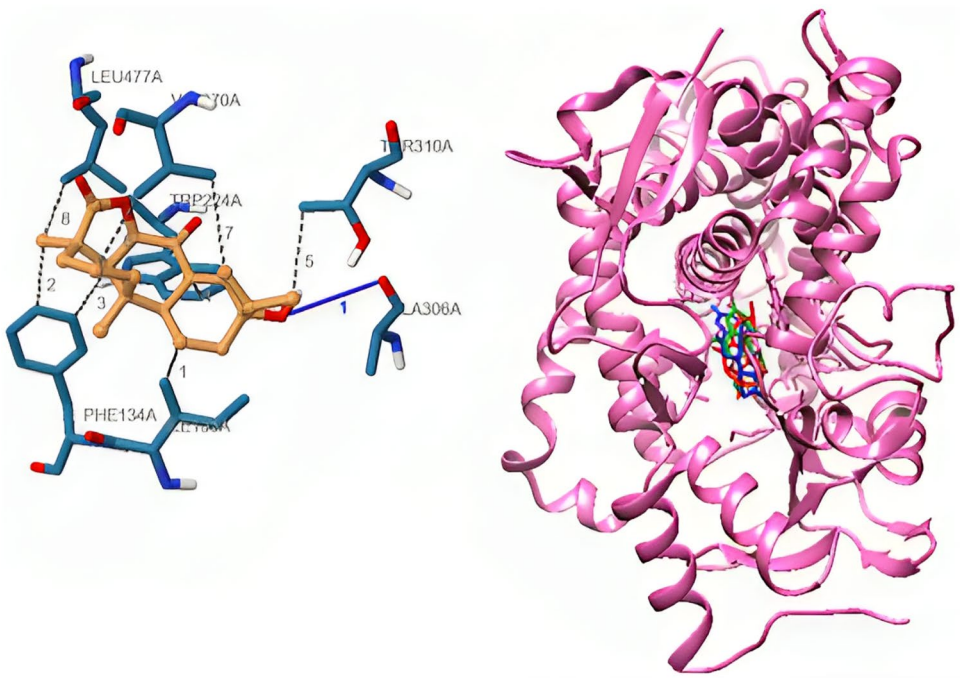

Fig. 1 Docked ligand comparison. The figure on the right presents 3s7s structure (Pink) with three ligands, the native exemestane (Blue), the redocked exemestane (Green), Juniperolide (Red). The figure on the top left presents Juniperolide (orang) bound to residues in the active site

Further assessment was performed to validate the accuracy of the docking by comparing the interactions in the native aromatase structure and the docked conformation. The same hydrogen bonds found in the native structure, Arg115 and Met374 were created by the redocked ligand. In addition, most of the hydrophobic interactions found in the native structure were also created by the redocked ligand, Ile133, Phe221, Leu477.

3.2 *Juniperus procera* phytochemicals-Aromatase interactions

The lowest binding energy and lowest inhibitory constant (KI) criteria were used to choose the best docked ligand molecules. The perfect docked conformation is the one that is created with the lowest binding energy since it has the highest affinity (Spontaneous binding and no additional energy input is required for the reaction to occur). The final configuration should be low energy because molecules in nature are typically found in their lowest energy state. Realizing these attributes is essential for the logical development of strong inhibitors [38].

Juniperolide, Kaurenoic acid and Isocupressic acid showed the highest interactions among the 124 compounds of *J. procera* with minimum binding energies of 11.33, 11.20 and 10.27 respectively, as appeared in Table 1. The binding affinity of Juniperolide and Kaurenoic acid was higher compared to the two anti-cancer drugs Arimidex and Femara and is almost similar to that of Exemestane. Juniperolide formed one hydrogen bond with residue Ala306 and several hydrophobic interactions with six residues, Ile133, Phe134, Trp224, Thr310, Val370 and Leu477. Kaurenoic acid formed two hydrogen bonds with residue Leu372 and Met374, several hydrophobic interactions with six residues, Ile133, Trp224, Ala306, Thr310, Val370 and Leu477, and one salt bridge with Arg115. Kaurenoic acid-Aromatase complex gave a lower binding affinity than Juniperolide-Aromatase complex, despite the presence of more interactions. This could be as a result of the ligand's energy being released in order to interact with the protein.

To further confirm the validity of the docking, the current results were compared with previous studies. Our redocking results for active site interactions were identical to those published by [39–41] although there were some differences in the preparation of input files and the grid box size. As far as we know, no in silico or laboratory experiments have been performed on the interactions of Juniperolide and Aromatase. Additionally, no prior research has been done on the interaction between Isocupressic acid and aromatase. In terms of Kaurenoic Acid, a review by [42] stated that while it was a very weakly docking ligand, it did demonstrate selective docking to aromatase. Apart from our finding that there is a possible inhibitory role of Juniperolide against Aromatase, there have been no laboratory experiments conducted on the activity of Juniperolide as anticancer compound. As for Kaurenoic Acid and Isocupressic acid, there are several laboratory studies that have proven the presence of anti-cancer effects of these two compounds [43–46].

3.3 Ligand–protein stability analysis

The stability and conformational changes of each aromatase-ligand complex was assessed through Normal Mode Analysis (NMA) using NMSim web server. NMSim is a geometric simulation method based on normal modes for investigating biologically significant protein structural changes. NMA results showed that RMSD per Residue of X-ray structure of aromatase was in good agreement with the Juniperolide-Aromatase complex (Fig. 2). The RMSD of all the atoms in each pair of residues in the two proteins was identical. According to these findings, the Juniperolide-Aromatase complex is stable, and the ligand has no impact on its stability. Similar results were observed for the Kaurenoic acid-Aromatase complex.

3.4 ADMET of compounds

The best docked compound and the control molecules' physicochemical properties are shown in Table 2. According to the bioinformatics findings, each of the six compounds had a good possibility of acting as an enzyme inhibitor. The best enzyme inhibitor scores were 0.86 for Exemestane and 0.73 for Isocupressic acid, respectively. The cytotoxicity scores for the three natural substances in Arar, Juniperolide, Kaurenoic acid, Isocupressic acid and the controls were inactive. The lowest ability to penetrate cell membranes is associated with molecules with a polar area greater than 140 Å [2] in Topological Polar Surface Area (TPSA). The compounds that were tested were all able to pass through cell membranes, and Exemestane and Kaurenoic acid were the most permeabilized. All six compounds were shown to have significant gastrointestinal absorption of the drug.

Several studies [47–49] have shown that Exemestane, Femara, and Arimidex have numerous negative effects as aromatase inhibitors. Even though numerous synthetic drugs are useful and correctly administered, many medicines have been discovered to cause harsh adverse effects [50]. In addition, the high toxicity usually associated with some cancer chemotherapy drugs and their undesirable side-effects increase the demand for natural anti-tumor drugs active against untreatable tumors, with fewer side-effects and/or with greater therapeutic efficiency [51]. Natural product-based medications seek to reduce several disadvantages associated with synthetic chemicals and conventional chemotherapy methods [52].

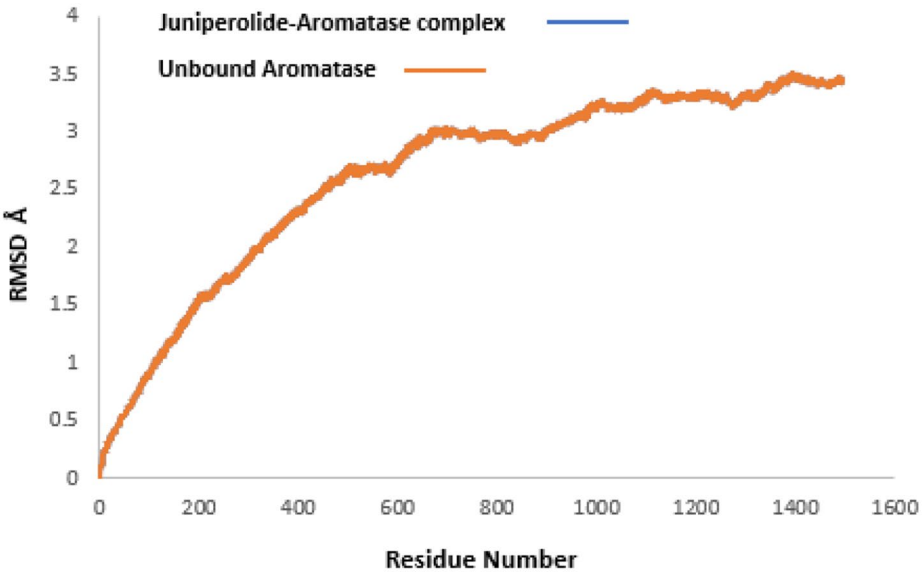

Fig. 2 RMSD plot of bound and unbound aromatase

Table 2 Physicochemical properties of compounds

Compound	Lipinski	GI absorption	TPSA (Å^2)	Enzyme inhibitor	Cytotoxicity
Exemestane	Yes; 0 violation	High	34.14	0.86	Inactive
Arimidex	Yes; 0 violation	High	78.29	0.12	Inactive
Femara	Yes; 0 violation	High	78.29	0.30	Inactive
Juniperolide	Yes; 0 violation	High	63.60	0.55	Inactive
Kaurenoic acid	Yes; 1 violation	High	37.30	0.46	Inactive
Isocupressic acid	Yes; 0 violation	High	57.53	0.73	Inactive

Our findings demonstrated that the three natural Arar compounds mentioned above can be used in place of Exemestane and the other two anti-cancer medications, Femara and Arimidex. Compared to synthetic medications, these natural substances may produce no negative effects or less side effects. The effectiveness of natural products as anti-cancer without significant side effects has been discussed in a number of scientific papers [53–55]. The fact that natural products are also metabolites gives them an advantage over synthetic molecules. As a result, they have biological activity and can serve as transporter system substrates [56].

4 Conclusion

As far as we are aware, this is the first investigation into potential inhibitory effects of *Juniperus procera* phytochemicals on the aromatase enzyme. Juniperolide, Kaurenoic acid, and Isocupressic acid were found to be more competitive aromatase inhibitors than FDA approved anticancer drugs, such as Exemestane, Arimidex, and Femara. To support our in silico findings, in vitro and in vivo experiments are still required.

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Data availability The datasets generated during and/or analyzed during the current study are available from corresponding author on reasonable request.

Declarations

Conflict of interest The author declares that he has no conflict of interest.

Ethical approval Not applicable for this article.

Human and animal rights It does not contain any studies with human or animal subjects.

Informed consent There are no human subjects in this article and informed consent is not applicable.

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