

ACKNOWLEDGMENTS

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ABSTRACT

Breast cancer is responsible for most of the women deaths in the world, this situation leads to the importance of the design of new drug candidates. On the same way severe side effects and non selectivity of some drugs make treatment sensitive and non effective. Drug discovery has significant role of finding of novel promising prodrugs that may progress to clinical trials in rapid evaluation process depend on prediction approaches.

This study aim to discover new hits of inhibitors of recent targets of breast cancer by using of bioinformatic technology to identify structure, conserved domain ,active site and physical and chemical properties of each target. Virtual screening of flavonoid compounds and zinc database compounds to find out active inhibitors. Testing of druglike properties in terms of chemical structure properties.

Computer-Assisted drug design(CADD) approach particularly structure based drug design was adopted to discover novel drug candidates of breast cancer. In this study, molecular operating environment (MOE) was used to run a post-docking simulation of zinc database compounds. The compounds had been docked before by DOCK6 of zinc.org server, a free database of commercially-available compounds for virtual screening(VS), ZINC database contains over 13 million purchasable compounds in ready-to-dock. Representatives of famous targets such as cyclooxygenases², Kinesin, Matrix Metalloproteinases⁹, Epithelial Growth Factor Receptor and Janus Kinase were chosen in docking simulations. Flavonoids and flavonoid derivatives also were selected according

to distinctive structures that have anticancer activity and were checked by docking simulation. Similar binding to the selected targets was observed.

The results predicted potential high and moderate anticancer activity as indicated by binding affinity comparable to drug standards. ZINC database compounds that had been selected exhibited moderate multitarget activity was less than that of the drug hence, less side effect is expected. Flavonoid derivatives compounds showed the same account of activity as well as preferred properties of lipiniski rule.

Quantitative Structure-Activity Relationship (QSAR) descriptors evaluated drug-likeness properties of compounds, namely $\log p$, water solubility, Lipinski drug-like test, reactive molecules, and molar refractivity.

ملخص البحث

سرطان الثدي هو المسئول عن الموت لمعظم النساء في العالم، وهذا الوضع يؤدي إلى أهمية تصميم دواء جديد. وبنفس القدر آثار جانبية شديدة وعدم الاختيارية لبعض الأدوية تجعل العلاج أكثر حساسية وغير فعال. اكتشاف العقاقير له دورا هاما في العثور على الأدوية الواعدة الحديثة التي يمكن تتقدم إلى تجارب سريرية في عملية التقييم السريعة التي تعتمد على طريقة الاستنباط.

وتهدف هذه الدراسة إلى اكتشاف مركبات جديدة من مثبطات المستقبلات الأخيرة من سرطان الثدي. باستخدام تكنولوجيا المعلوماتية الحيوية لتحديد البنية التركيبية، المحتوي الوظيفي، موقع نشط والخصائص الفيزيائية والكيميائية لكل مستقبل. استخدمت المعلوماتية الكيميائية باستخدام الفحص الظاهري للمركبات الفلافونويدية ومركبات قاعدة بيانات الزنك لمعرفة المثبطات الفعالة. كما تم اختبار الصفات الدوائية بالنسبة للتركيب الكيميائي.

صممت الأدوية باستخدام الكمبيوتر علي الاخص الطريقة التي تعتمد علي البنية التركيبية لاكتشاف عقاقير جديدة لمرض سرطان الثدي. في هذه الدراسة تم استخدام برنامج التشغيل الجزيئي لتشغيل محاكاة الارتباط لمركبات قاعدة بيانات الزنك والتي تمت محاكاة ارتباطها باستخدام برنامج دوك6 الخاص بالمستخدم الالكتروني زنك وهي قاعدة بيانات مجانية من المركبات المتاحة تجاريا للفحص الظاهري وتحتوي علي اكثر من ثلاثة عشر مليون مركب متاحة لاختبار محاكاة الارتباط. تم اختيار عينات لمستقبلات الادوية المضادة للسرطان المشهورة لمحاكاة الارتباط وهي:..

Cyclooxygenase2 ,Kinesin, Matrix Metalloproteinase9,Epithelial Growth Factor

Receptor and Janus Kinase

تم اختيار فلافونيدات و مشتقات الفلافونيدات أيضا وفقا للهياكل المميزة التي لهانشاط مضاد للسرطان وتم فحصها بمحاكاة الارتباط وقد لوحظ ان هنالك تشابه في ارتباطها بالمستقبلات.

اظهرت النتائج المستنبطة النشاط العالي والمتوسط المضاد للسرطان بالارتباط بالمستقبلات الذي يمكن مقارنته بالارتباط بالادوية. مركبات قاعدة بيانات الزنك التي تم اختيارها أظهرت النشاط متعدد المستقبلات معدل أقل

من الدواء الذي قد يؤدي إلى تأثير أقل الجانبية. وأظهرت المشتقات الفلافونويدية نفس القدر من النشاط وكذلك الخصائص المفضلة حسب قانون ليبينسكي.

تم تقييم خصائص مشابهة الادوية للمركبات بعناصر وصف العلاقة الكمية للنشاط بالبنية التركيبية وهي: معامل التوزيع بين الماء والكحول الثماني ، الذوبان في الماء ، اختبار خاصية الدواء ، الجزيئات المتفاعلة والانكسارية المولية.

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List of Publication

1-Accepted Papers

Accepted from The International Journal of Interdisciplinary Research and Innovations.

1-1 Computer Aided Drug Design Of New Inhibitors Of Tyrosine Kinase ; Epethlial Growth Factor as Breast Cancer Target.

Sumaya Osman, ,Amal Al-Aboudi and Abd- Alwahab Hassan.

1-2- *In Silico* Structure Insight and Discovery of Novel Inhibitors of Cyclooxyge- nase2 ;Potential Anticancer Agents.

Sumaya Osman, , Amal Al-Aboudi and Abd Alwahab Hassan

2-Papers under Preparation;

1-In Silico Approach of Inhibition of Matrix Matalloproteinase9 as Metastasis agent.

2-Novel Inhibitors of Janus Kinase; Specific Agent of Breast Cancer.

3- Kinesin Motor Inhibitors ; Hits of cancer Drug Candidates.

List of Abbreviations

CADD	Computer- Assisted Drug Design
MOE	Molecular Operating Environment
HTS	Highthroughput Screening
VS	Virtual Screening
COX2	Cyclooxygenase2
MMP9	Matrix Metalloproteinase9
EGFR	Epithelial Growth Factor Receptor
JAK2	Janus Kinase 2
QSAR	Quantitative Structure Activity Relationship
HER2	Human Epithelial Receptor2
DNA	Deoxyribonucleic Acid
MPA	Mycophenolic
CDK	Cyclin-Dependant Kinase
TCA	Tricarboxylic cycle Acid (Krebs)
CHS	Chalcone Synthase
C4H	Cinnamate-4-Hydroxylase

CHI	Chalcone Isomerase
CHR	Chalcone Reductase
CHS	Chalcone Synthase
4CL4	-Coumaroyl:CoA-Ligase
DFR	Dihydroflavonol 4-Reductase
DMID	7,29-Dihydroxy, 49-Methoxyisoflavanol Dehydratase
F3H	Flavanone 3-Hydroxylase
FSI,FSII	Flavone Synthase
F39H	Flavonoid 39 hydroxylase
F3959H	Flavonoid 3959 Hydroxylase
IOMT	IsoflavoneO-Methyltransferase
IFR	Isoflavone Reductase
I29H	Isoflavone29- Hydroxylase
IFS	Isoflavone Synthase
LDOX	Leucoanthocyanidin Dioxygenase
LCR	LeucoanthocyanidinReductase
OMT	O-Methyltransferase
PAL	Phe ammonia-lyase

RT	Rhamnosyl Transferase
STS	Stilbene Synthase
UFGT	UDPGflavonoidglucosyl transferase
VR	Vestitone Reductase
EGCG	Epigallocatechin-3-GALLATE
VEGF	Vascular Endothelial Growth Factor
HGF	Hepatocyte Growth Factor
K_d	Dissociation Equilibrium Constant
QSPR	Quantitative Structure-Property Relationship
CSCs	Cancer Stem-like Cells
SiRNA	SignalRibonucleic Acid
ER	Estrogen Receptor
BTK	Bruton's tyrosine kinase
MLK	Mixed-Lineage Kinase
Drp1	Dynamin-related protein 1
GPNMB	Glycoprotein non-metastatic B
PGs.	Prostaglandins
TX	Thromboxane

KHC	Kinesin Heterotetrameric Chains
KLC	Kinesin Light Chains
TIMP	Tissue Inhibitors Of Metalloproteinases
TK	Tyrosine Kinase
RTK	Receptor tyrosine kinase
ErbB2	Epithelial receptor member b -B2
STATs	Signal Transducer and Activator of Transcription
TNBCs	Triple-Negative Breast Cancers
NCBI	National Center for Biotechnology Information
E.C	Enzyme Code
E.A	Enzyme Accession
BLAST	Basic Local Alignment Search Tool
RCSB	Research Collaborator for Structural Bioinformatics
PDB	Protein Data Bank
PGHS	Prostaglandin H₂Synthase
Cb	Calcium-binding
Kif2	Kinesin Family member 2A
ADP	Adenosine Diphosphate

ATP	Adenosine Triphosphate
CD	Conserved Domain
PTK	Protein Tyrosine Kinase
RIO	serine/threonine protein kinase
MgATP	Magnesium Adenosine Triphosphate
IFNs	Interferons
PCA	Principal component analysis
LogP	Log of the octanol/water partition coefficient
LogS	Log of the aqueous solubility (mol/L).
EAC	Ehrlich Ascites Carcinoma
ROS	Radical Oxygen Species)
ARG	Arginine
GLU	Glutamate
LYS	Lysine
TYR	Tyrosine
PRO	Proline
HIS	Histidine
LEU	Leucine

GLN	Glutamine
CYS	Cysteine
ASP	Aspartate
THR	Threonine
MET	Methionine
SER	Serine
GLY	Glycine
ASN	Asparagine

