IJPSR (2023), Volume 14, Issue 5 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 24 August 2022; received in revised form, 14 October 2022; accepted 14 November 2022; published 01 May 2023

COMPUTATIONAL ANALYSIS OF PHARMACOKINETICS, BIOACTIVITY AND TOXICITY PROFILING OF SOME SELECTED OVULATION-INDUCTION AGENTS TREATING POLYCYSTIC OVARY SYNDROME (PCOS)

Divya Bisht *, Deena Prakash and Arvind Kumar Shakya

School of Sciences, Indira Gandhi National Open University, Maidan Garhi - 110068, New Delhi, India.

Keywords:

PCOS, Ovulation induction drugs, Bioactivity, TPSA

Correspondence to Author:
Ms. Divya Bisht

Research Scholar,
School of Sciences, Indira Gandhi National Open University, Maidan Garhi - 110068, New Delhi, India.

E-mail: divyabisht489@gmail.com

ABSTRACT: PCOS (Polycystic ovarian syndrome) is a prevalent female endocrine disorder with global occurrence ranging from 6-26%. It accounts for the majority of anovulatory infertility in women of reproductive age due to enlarged ovaries with small cysts formation, which the National Institute of Health has reported as a cause of 30% of infertility cases in females worldwide. Anovulatory infertility is generally treated with ovulation induction therapy using drugs to promote and facilitate ovulation. However, these medications' varying success rates and numerous adverse effects compel the search for more promising and safer alternatives. In this research study, 10 ovulation induction agents *i.e.*, Tamoxifen, Metformin, Clomiphene, Pioglitazone, Letrozole, Rosiglitazone, Anastrozole, Prednisone, Dexamethasone, and Spironolactone, were selected to analyze their pharmacokinetics, drug-likeness, bioactivity profile, and toxicity profile through the *in-silico* approach. The results present information about each drug, including its pharmacological competency and level of toxicity. This study may aid in the direction of future research and the development of more effective ovulation-inducing medications.

INTRODUCTION: Polycystic ovary syndrome (PCOS) is a complex heterogeneous endocrine disorder prevailing globally, affecting women in their premenopausal years. Stein and Laventhal discovered it in 1935 after observing symptoms such as hirsutism, obesity, multiple ovarian cysts, and amenorrhea in women and researching how they might be linked [1]. PCOS generally causes hormonal imbalance in women by increasing male hormone levels (hyper-androgenism) and promoting the growth of ovarian cysts, both of which impair the body's metabolism and reproductive function.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.14(5).2522-26

This article can be accessed online on www.ijpsr.com

DOI link: http://doi.org/10.13040/IJPSR.0975-8232.14(5).2522-26

The actual etiology of PCOS is unknown; however, it is assumed to be caused by a poor lifestyle, lack of exercise, nutritional imbalance, and stress, as well as certain environmental and hereditary factors [2, 3]. PCOS symptoms include increased body weight, thick hairs on the face and body (Hirsuitism), acne, mood swings, menstrual dysfunction, and numerous cysts in the ovaries [4]. Depending on the diagnostic criteria employed and the demographic analyzed, the global prevalence of this illness ranges from 6% to 26% [5-9]. It raises the risk of infertility, diabetes, and cardiovascular disease [10, 11].

PCOS causes ovulatory dysfunction, leading to anovulatory infertility due to irregular menstruation, blockage in the creation and release of the ovum, elevated levels of male hormone (androgens) in the ovary, altered gonadotropin dynamics, obesity, and insulin resistance (*i.e.*, the lack or absence of ovulation) [12].

PCOS is responsible for more than 90% of cases of anovulatory infertility [13]. Ovulation induction therapy, which uses various drugs and hormonal agents to increase the chances of ovulation and successful pregnancy, treats infertility in women with anovulation. However, these drugs have numerous side effects, have a variable therapeutic success rate, and fail to cure the disease's root cause. This raises concern about developing new drugs with greater therapeutic potential. The current study uses computational methods to analyze parameters such as pharmacokinetics, bioactivity score, and toxicity profile for some selected ovulation induction agents used in treating PCOS, namely, Tamoxifen, Metformin, Clomiphene, Pioglitazone, Letrozole, Rosiglitazone, Anastrozole, Prednisone, Dexamethasone, and Spironolactone. The outcomes of this study will aid in developing and discovering new and better medications in the future.

MATERIALS AND METHODS:

Data Content: The current investigation was carried out by conducting a thorough and coordinated search of the existing literature on specific ovulation induction drugs. Google Scholar (http://www.scholar.google.com) and PubChem (https://pubchem.ncbi.nlm.nih.gov) were used for the searches.

***In-silico* Pharmacokinetic Studies:** The Molinspiration Chemoinformatics server (http://www.molinspiration.com) was used to calculate the physicochemical descriptors and pharmacokinetic relevant properties of selected ovulation induction agents. This server offers a wide range of chemoinformatics software tools to help with molecule manipulation and processing. SMILES and SD file conversion, molecule normalization, tautomer generation, molecule fragmentation, QSAR molecular properties calculation, molecular modeling and drug design, high-quality molecule depiction, and molecular database tools supporting substructure and similarity searches are all included. This software allows virtual screening based on fragments, bioactivity prediction, and data visualization. Drug-likeness was used to screen the similarity between a specific molecule and a known drug using a set of structural features and various molecular properties to select potential drug candidates. It was calculated using the Lipinski rule of five (RO5), which deals with four simple physicochemical parameter ranges (MWT 500, log P 5, H-bond donors 5, H-bond acceptors 10) associated with 90% of orally active drugs that have passed phase II clinical status [14]. Other evaluation methods, such as ligand and lipophilic efficiency, were also used to express drug-likeness as potency parameters, which are associated with aqueous solubility and intestinal permeability within an acceptable range.

***In-silico* Bioactivity Studies:** The bioactivity score for the selected ovulation induction agents was evaluated using the Molinspiration Chemoinformatics server (http://www.molinspiration.com) as it efficiently balances screening time and accuracy, initial information input, and screening performance. The miscreen built-in functionality in Molinspiration creates a virtual screening model for any target and analyses it using Bayesian statistics. GPCR ligand, ion channel modulator, kinase inhibitor, nuclear receptor ligand, protease inhibitor, and enzyme inhibitor activity scores are used to calculate the bioactivity score. The higher the activity score, the more likely a molecule is to be active. This aids in the discovery of new and improved drug candidates.

***In-silico* Toxicity Study:** The toxicity of selected ovulation induction agents was calculated using the admet SAR tool by entering each agent's SMILES notation [15]. Admet SAR is a web-based service that allows you to screen and evaluate chemical profiles such as absorption, distribution, metabolism, excretion, and toxicity.

It predicts up to 50 ADMET endpoints using an advanced chemoinformatics-based toolbox called ADMET-Simulator, which generates accurate QSAR models. It provides information on the drug's induced toxicity, hepatotoxicity, AMES toxicity, carcinogenicity, eye corrosion, and eye irritation, as well as whether the drug adheres to Lipinski Rule [16].

RESULTS AND DISCUSSION: Table 1 shows the ADME properties and drug-likeness (Lipinski's rule of five) of ten ovulation induction drugs (Tamoxifen, Metformin, Clomiphene, Pioglitazone, Letrozole, Rosiglitazone, Anastrozole, Prednisone,

Dexamethasone, and Spironolactone). The molecular weight of all selected agents was in the acceptable range *i.e.*, MWT ≤ 500. Low molecular weight molecules are more suitable for drug formation due to their better absorption, diffusion, and transportation capacity. The MLogP (octanol/ water partition coefficient) of all agents was found to be within acceptable range *i.e.* MLogP ≤ 4.15 according to Lipinski's rule except Tamoxifen with MLogP 6.06 and Clomiphene with MLogP 6.53. Tamoxifen and Clomiphene have one violation of Lipinski's rule of five with a high MLogP value out of ten selected ovulation induction agents. The lipophilic efficiency is calculated using the MLogP value to assess drug potency.

The logP value also determines the hydrophobicity of molecules, which is necessary for drug absorption in the body. The polarity of compounds determines drug transport property *via* TPSA (Topological Polar Surface Area) value. The total polar surface area is the sum of all polar atoms. The formula was also used to calculate the percent absorption of all agents [percent ABS = 109-(0.345 * TPSA)]. Molecular volume is used to investigate molecular transport properties such as blood-brain barrier penetration. The number of rotatable bonds was also found to be advantageous, as the greater the number of rotatable bonds, the greater the flexibility and binding affinity with the binding pocket.

TABLE 1: ADME PROPERTIES OF OVULATION-INDUCTION AGENTS

Name	Molecular Formula	Molecular Weight (g/mol)	LogP	TPSA	nON	nOHNH	nrotb	Volume	*In-silico*% Absorption
Tamoxifen	C26H29NO	371.52	6.06	12.47	2	0	8	376.13	96.18
Metformin	C4H11N5	129.17	-1.26	91.50	5	5	2	126.68	77.43
Clomiphene	C26H28ClNO	405.97	6.53	12.47	2	0	9	389.91	96.18
Pioglitazone	C19H20N2O3S	356.45	3.07	68.30	5	1	7	318.53	85.44
Letrozole	C17H11N5	285.31	2.15	78.30	5	0	3	254.46	81.99
Rosiglitazone	C18H19N3O3S	357.44	2.35	71.53	6	1	7	314.51	84.32
Anastrozole	C17H19N5	293.37	2.85	78.30	5	0	4	282.28	81.99
Prednisone	C21H26O5	358.43	1.41	91.67	5	2	2	331.01	77.37
Dexamethasone	C22H29FO5	392.47	2.06	94.83	5	3	2	358.07	76.28
Spironolactone	C24H32O4S	416.6	3.03	60.45	4	0	2	387.63	88.14

The bioactivity of all ten selected ovulation induction agents was determined against six different protein structures. Bioactivity score is used to measure biological activity and is categorized under three different ranges:

Bioactivity score > 0.00, considerable biological activity. Bioactivity score = (0.5 - 0.00), moderate biological activity. Bioactivity score<-0.50, inactivity. The bioactivity score profile of all selected agents is shown in **Table 2**.

TABLE 2: BIOACTIVITY OF OVULATION-INDUCTION AGENTS

Name	GPCR Ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
Tamoxifen	0.30	0.00	-0.01	0.57	0.04	0.32
Metformin	-1.61	-0.93	-2.38	-3.21	-1.39	-1.23
Clomiphene	0.15	-0.17	-0.20	0.16	-0.16	0.07
Pioglitazone	0.25	-0.51	-0.71	0.64	-0.09	0.05
Letrozole	-0.06	-0.07	-0.19	-0.27	-0.24	0.30
Rosiglitazone	0.15	-0.65	-0.61	0.35	-0.21	-0.07
Anastrozole	0.10	-0.04	-0.05	-0.40	-0.14	0.12
Prednisone	0.02	-0.12	-0.81	1.00	0.06	0.63
Dexamethasone	0.03	-0.21	-0.81	1.59	0.76	0.78
Spironolactone	-0.07	-0.19	-0.91	1.15	0.15	0.53

The findings imply that the chosen agents are biologically active and have physiological effects. This bioactivity score information can be used to develop new drugs with greater efficacy and binding capacity. **Table 3** shows the toxicity profile of all selected ovulation induction agents. Except for Metformin, Prednisone, Dexamethasone, and Spironolactone, most drugs cause hepatotoxicity. Tamoxifen has a high carcinogenicity. Acute oral toxicity is classified according to the US EPA

criterion, with Category I is with LD_{50} value of 50mg/kg, Category II is with LD_{50} value greater than 50mg/kg but less than 500mg/kg, Category III is with LD50 value greater than 500mg/kg. Category IV is with LD_{50} value greater than 500mg/kg but less than 5000mg/kg.

CONCLUSION: All ovulation induction drugs showed significant ADME properties and drug likeness along with considerable biological activity and physiological effects. However six out of ten selected ovulation induction drugs were found to be hepatotoxic making them less suitable for administration.

Thus, the findings of this study will aid in the development of better and more potent ovulation induction drugs with low toxicity for the treatment of an ovulation infertility caused by PCOS in the future.

TABLE 3: TOXICITY PROFILE OF OVULATION-INDUCTION AGENTS

Name	Human Ether-a-go-go-Related Gene Inhibition	AMES Toxicity	Acute Oral Toxicity	Carcino-genicity	Hepato-toxicity	Eye Corrosion	Eye irritation
Tamoxifen	Strong	Non-Toxic	III	High	Toxic	Nil	Nil
Metformin	Weak	Non-Toxic	III	Nil	Non-Toxic	Nil	Present
Clomiphene	Strong	Non-Toxic	IV	Nil	Toxic	Nil	Nil
Pioglitazone	Weak	Non-Toxic	III	Nil	Toxic	Nil	Nil
Letrozole	Weak	Non-Toxic	III	Nil	Toxic	Nil	Nil
Rosiglitazone	Weak	Non-Toxic	III	Nil	Toxic	Nil	Nil
Anastrozole	Weak	Non-Toxic	III	Nil	Toxic	Nil	Nil
Prednisone	Weak	Non-Toxic	III	Nil	Non-Toxic	Nil	Nil
Dexamethasone	Weak	Non-Toxic	III	Nil	Non-Toxic	Nil	Nil
Spironolactone	Weak	Non-Toxic	III	Nil	Non-Toxic	Nil	Nil

ACKNOWLEDGMENT: The Corresponding author Ms. Divya Bisht expresses thanks to the DST Inspire Division, Department of Science and Technology, New Delhi, India, for providing financial support in the form of DST INSPIRE Fellowship and special thanks to Dr. Arvind Kumar Shakya, Assistant Professor, Biochemistry, School of Sciences, Indira Gandhi National Open University, New Delhi-110068 for providing help in experimental work of bioinformatics tools and finalize the manuscript.

CONFLICTS OF INTEREST: The authors hereby declare that there is no conflict of interest.

REFERENCES:

1. Koçak Ö and Senel E: A scientometric analysis on Polycystic Ovarian Syndrome Between 1975 and 2018. Ejons International Journal 2022; 6(21): 179–192.
2. Jiskoot G, Timman R, Beerthuizen A, Dietz de Loos A, Busschbach J and Laven J: Weight reduction through a cognitive behavioral therapy lifestyle intervention in PCOS: the primary outcome of a randomized controlled trial. Obesity 2020; 28(11): 2134-2141.
3. Zehra B and Khursheed AA: Polycystic ovarian syndrome: symptoms, treatment and diagnosis: a review. Journal of Pharmacognosy and Phytochemistry 2018; 7:875–880.
4. Varughese AK and Greetta TV: Polycystic Ovarian Syndrome-An Overview. International Journal of Nursing Education and Research 2019; 7(4): 601-604
5. Choudhary A, Jain S and Chaudhari P: Prevalence and symptomatology of polycystic ovarian syndrome in Indian women: is there a rising incidence. International Journal of Reproduction, Contraception Obst and Gyne 2017; 6(11): 4971.
6. Lauritsen MP, Bentzen JG, Pinborg A, Loft A, Forman JL, Thuesen LL, Cohen A, Hougaard DM and Nyboe Andersen A: The prevalence of polycystic ovary syndrome in a normal population according to the Rotterdam criteria versus revised criteria including anti-Mullerian hormone. Human Reproduction 2014; 29(4): 791-801.
7. Deswal R, Narwal V, Dang A and Pundir CS: The Prevalence of Polycystic Ovary Syndrome: A Brief Systematic Review. Journal of Human Reproductive Sciences 2020; 13(4): 261–271.
8. Kakoly NS, Khomami MB, Joham AE, Cooray SD, Misso ML, Norman RJ, Harrison CL, Ranasinha S, Teede HJ and Moran LJ: Ethnicity, obesity and the prevalence of impaired glucose tolerance and type 2 diabetes in PCOS: a systematic review and meta-regression. Human Reproduction Update 2018; 24(4): 455–467.
9. Skiba MA, Bell RJ, Herbert D, Garcia AM, Islam RM and Davis SR: Use of community-based reference ranges to estimate the prevalence of polycystic ovary syndrome by the recognised diagnostic criteria, a cross-sectional study. Human Reproduction 2021; 36(6): 1611–1620.
10. Hoeger KM, Dokras A and Piltonen T: Update on PCOS: Consequences, Challenges, and Guiding Treatment. The J of Clinical Endo & Metabolism 2021; 106(3): 1071-1083.
11. Zhu T, Cui J and Goodarzi MO: Polycystic Ovary Syndrome and Risk of Type 2 Diabetes, Coronary Heart Disease, and Stroke. Diabetes 2021; 70(2): 627–637.
12. Frydenberg H: The Treatment of Obesity in Polycystic Ovary Syndrome. In: Polycystic Ovary Syndrome. G. Kovacs, B. Fauser and R. Legro(ed.), Cambridge University Press 2022; 150-161.
13. Li M, Ruan X and Mueck AO: Management strategy of infertility in polycystic ovary syndrome. Global Health Journal 2022; 6(2): 70-74.

14. Sliwoski G, Kothiwale SK, Meiler J and Lowe EW: Computational Methods in Drug Discovery. Pharmacological Reviews 2014; 66 (1): 334-395;
15. Kar S, Roy K and Leszczynski J: *In-silico* Tools and Software to Predict ADMET of New Drug Candidates. In: *In-silico* Methods for Predicting Drug Toxicity. Methods in Molecular Biology. E. Benfenati(ed.), Humana, New York 2022; 2425.
16. Yang H, Sun L, Wang Z, Li W, Liu G and Tang Y: ADMETopt: A Web Server for ADMET Optimization in Drug Design *via* Scaffold Hopping. Journal of Chemical Information and Modeling 2018; 58(10): 2051–2056.

How to cite this article:
Bisht D, Prakash D and Shakya AK: Computational analysis of pharmacokinetics, bioactivity and toxicity profiling of some selected ovulation-induction agents treating polycystic ovary syndrome (PCOS). Int J Pharm Sci & Res 2023; 14(5): 2522-26. doi: 10.13040/IJPSR.0975-8232.14(5).2522-26.