

Computational profiling of antidepressants-induced molecular docking with placental proteins (IGFBP-1, PlGF-1 and GATA3)

By Sarah T. Al-Saray

Computational profiling of antidepressants-induced molecular docking with placental proteins (IGFBP-1, PlGF-1 and GATA3)

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ABSTRACT

Background: Antidepressants readily penetrate the intrauterine environment, potentially influencing the genetic expression of specific genes in the fetal portion of the placenta. Nevertheless, there is a lack of understanding regarding the precise impact of these medications on placental proteins, which play critical roles in embryonic development.

Methods: Therefore, investigating their interaction with antidepressants becomes crucial. Utilizing computational analysis and molecular docking software, this study explores the interactions between ten antidepressant medications and the proteins IGFBP-1, PlGF-1, and GATA3 through dynamic simulation.

Results: The findings from molecular docking reveal a clear inclination of all drugs to bind with these proteins, albeit with varying degrees of affinity. Certain drugs (Trazodone, Amitriptyline, Nortriptyline, and Mirtazapine) exhibit high affinities for these proteins, while others show lower affinities (Desvenlafaxine, Phenelzine, and Tranylcypromine). The affinity values for IGFBP-1 and PlGF-1 ranged from -6.80 to -3.90 kcal/mol, with an average of -5.90 kcal/mol. In comparison, the affinity range for the GATA3 protein was -7.80 to -5.10 kcal/mol.

Conclusion: Following the molecular dynamic simulation of the four drugs exhibiting high affinity to proteins, it became evident that they did not maintain stability within acceptable limits during the simulation, except for Trazodone. Interestingly, Trazodone showed signs of stabilization with the IGFBP-1 protein throughout the molecular dynamic simulation. These findings may indicate that Trazodone potentially influences embryonic development, raising safety concerns for maternal-fetal health. Choosing the safest medications, considering both mental health and potential molecular influences, is crucial for maternal and fetal well-being during pregnancy. Further research and clinical guidelines should explore the interplay between antidepressant affinities and maternal-fetal health outcomes for a more informed approach to perinatal mental health care.

Key Words: Molecular Docking, Antidepressants, Placental Proteins, IGFBP-1, PlGF-1, GATA3

Introduction

Depression recognized as a pathological condition, stands as the most prevalent mental health disorder in women, particularly during pregnancy [1-3]. Peripartum mental disorders, such as anxiety and

depression, are widespread, with maternal depression being linked to adverse outcomes. ² Antepartum anxiety and depression exhibit distinct and cumulative negative effects on both maternal and fetal outcomes [4-7]. Consequently, effective treatment for maternal depression may necessitate the use of antidepressant medications [3,8-9]. In light ¹⁰ of the elevated prevalence of depression among pregnant women, exploring ⁸ the intricate connection between this mental health condition and the indispensable use of antidepressant medications becomes imperative. This exploration is particularly crucial in unraveling the potential impacts of antidepressants on essential placental proteins. Antidepressant medications, particularly those falling under the ⁸ selective serotonin reuptake inhibitors (SSRIs) class, are known to cross the human placenta [10], thereby impacting neonatal health [11]. Antidepressants can impact fetal growth and contribute to the development of congenital malformations by influencing the occurrence of genetic mutations and altering ⁸ the characteristics of proteins [12-13]. Recently, increased attention has been directed toward exploring ³ the potential connection between perinatal antidepressant consumption and adverse neonatal outcomes [4,14-17]. Recognizing the importance of pregnant women taking antidepressants to protect both themselves and their fetuses, the careful selection of the most ³ appropriate medication is crucial. In recent years, there has been a growing focus on investigating ³ the potential link between perinatal antidepressant consumption and adverse neonatal outcomes. This study specifically delves into the effects of ten antidepressant medications on three human placental proteins: IGFBP-1, PIGF-1, and GATA3, through computational analysis. ¹¹ IGFBP-1 (Insulin-like Growth Factor Binding Protein-1) is integral ⁹ to embryogenesis, orchestrating the activity of insulin-like growth factors (IGFs) such as IGF-I and IGF-II. By binding to IGFs, IGFBP-1 modulates their availability and activity, impacting critical processes in embryonic development, including cell proliferation, differentiation, and survival¹⁶ [18]. ⁶ PIGF-1 (Placental Growth Factor-1), a member of the Vascular Endothelial Growth Factor (VEGF) family, emerges as a key player in placental development and angiogenesis. Expressed in the placenta, PIGF-1 actively promotes angiogenesis, a vital process for both ¹⁷ embryonic development and post-natal growth. Its interactions with VEGF receptors underscore its significance in regulating blood vessel growth during pregnancy [19-20]. GATA binding protein 3 (GATA3), part of the transcription factor family, assumes a pivotal role in embryogenesis, contributing diverse functions to the development of various tissues and organs. From critical involvement in inner ear development to essential roles in kidney development, immune system maturation, breast development, cardiac development, and neural tube development, GATA3 emerges as a multifaceted regulator. Expressed in the placenta, it influences trophoblast cell differentiation and function. GATA3's context-dependent role

in gene regulation is fundamental for the proper differentiation and function of diverse cell types during embryogenesis [21-22]. Overview of the functions and regulatory mechanisms of IGFBP-1, PIGF-1, and GATA3 in embryonic development encapsulates the roles these proteins play in fundamental biological processes. To delve into the molecular intricacies of this phenomenon, our study employs advanced computational analysis, focusing on the effects of ten antidepressant medications on three key human placental proteins: IGFBP-1, PIGF-1, and GATA3. This nuanced approach aims to uncover the underlying molecular mechanisms, paving the way for a comprehensive understanding of the potential impact on embryonic development.

Material and Methods

The chemical structures of the drug molecules examined in the study were obtained from the Zinc 15 database website (Figure 1 A). Before initiating the molecular docking process, the ligands were prepared using the Virtual Screening Tool Python Prescription program (Version: PyRx-0.8), and the energy minimization parameters were set as follows: Force Field: uff, Optimization Algorithm: Conjugate Gradients, Total number of steps: 200, Number of steps for update: 1, Stop if energy differences are less than: 0.1. The human placenta proteins studied were acquired from the Protein Data Bank website using the following identifiers (IGFBP-1 ID: 1zt3, PIGF-1 ID: 1fzv, GATA3 ID: 4hc9) (Figure 1 B). These proteins were then cleaned and prepared for the molecular docking process using the Discovery Studio software. The target functional site for each protein was determined as follows: The C-terminal domain for IGFBP-1 [23], the PIGF-1zFlt-1D2 complex for PIGF-1 [24], and the C-terminal zinc finger for GATA3 [25]. Molecular docking was performed using PyRx-0.8, and the Discovery Studio software was utilized to illustrate the interactions and binding sites between the proteins and the drugs studied. Following molecular docking, molecular dynamics simulations of the candidate drugs were conducted using the Schrödinger program. These simulations spanned a duration of up to 100 nanoseconds for both proteins and drugs.

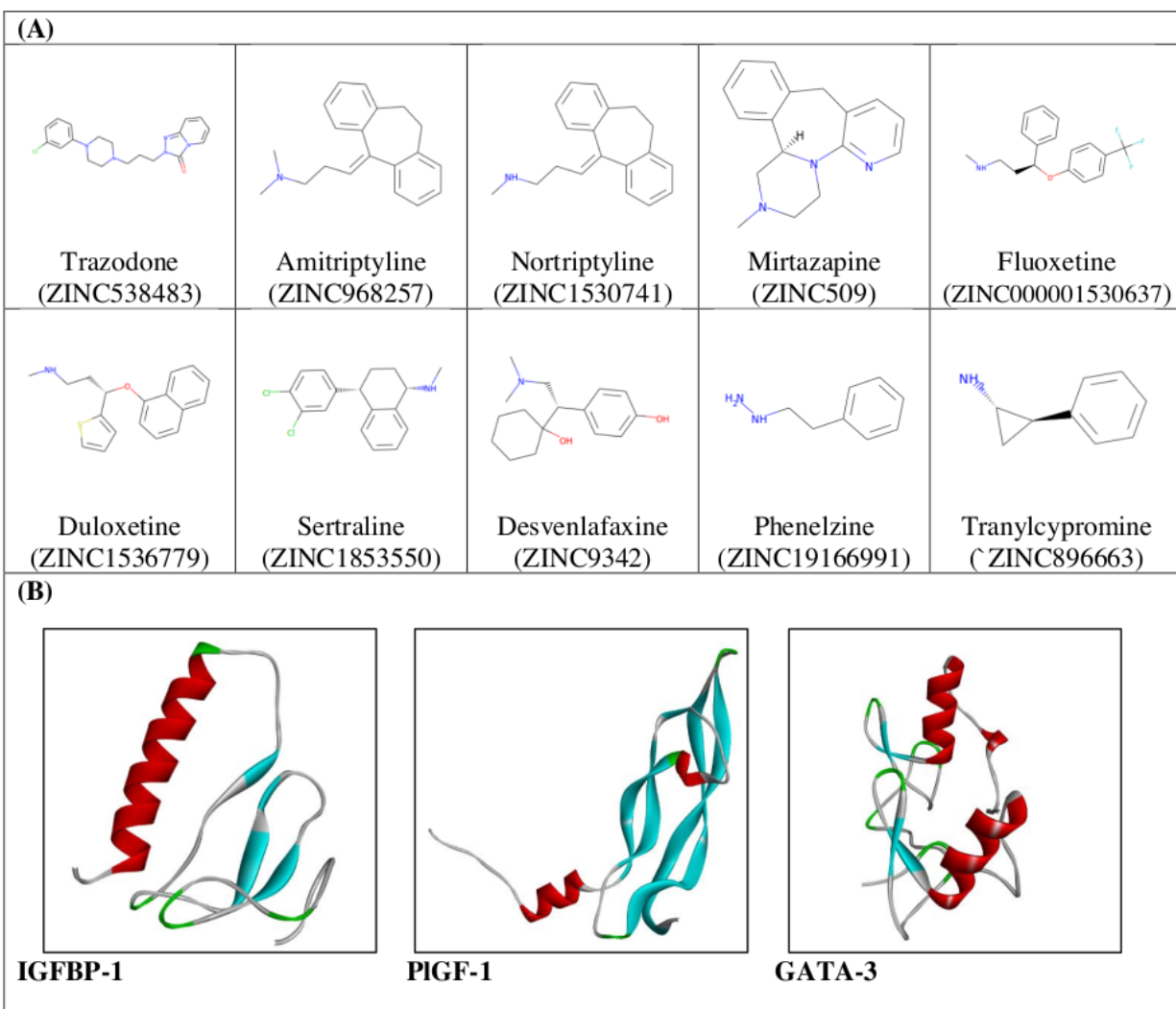


Figure 1: (A) Depicts drug compositions obtained from the ZINC15 website, and (B) illustrates the structures of proteins obtained from the PDB Protein Data Bank website.

Results

Molecular Docking

Furthermore, each of the three proteins engaged in numerous bonds with the antidepressant drugs, showcasing diversity in both type and number. Predominantly, these interactions manifested as traditional hydrogen bonds, non-traditional hydrogen bonds, and various other bond types such as van

der Waals, Pi-Pi stacked, Alkyl, as detailed in Table 1-3 and illustrated in Figure 2. The average number of bonds formed by the proteins with drugs was (5), (4), and (6) for IGFBP-1, PIGF-1, and GATA3 proteins, respectively, as summarized in Table 1-3 and visualized in Figure 2. Observations revealed that Trazodone, Amitriptyline, Nortriptyline, and Mirtazapine exhibited the highest affinity kcal/mol. respectively for the IGFBP-1 protein (Table 1, Figure 2). Similarly, concerning the PIGF-1 and GATA-3 proteins, these drugs exhibited the highest affinity values, graded as follows: Trazodone, Nortriptyline, Mirtazapine, and Amitriptyline (Table 1-2, Figure 2). Furthermore, the findings indicated that Desvenlafaxine, Phenelzine, and Tranylcypromine exhibited the lowest affinity values kcal/mol. for both the IGFBP-1 and GATA-3 proteins. Similarly, with respect to the PIGF-1 protein, these drugs displayed the least affinity values in the following order: Desvenlafaxine, Tranylcypromine, and Phenelzine (Table 1-2, Figure 2). Having unveiled the intricate interactions and affinity patterns between antidepressant medications and the key placental proteins, the ensuing discussion delves into the nuanced implications of these findings, shedding light on their potential significance for maternal health and fetal development.

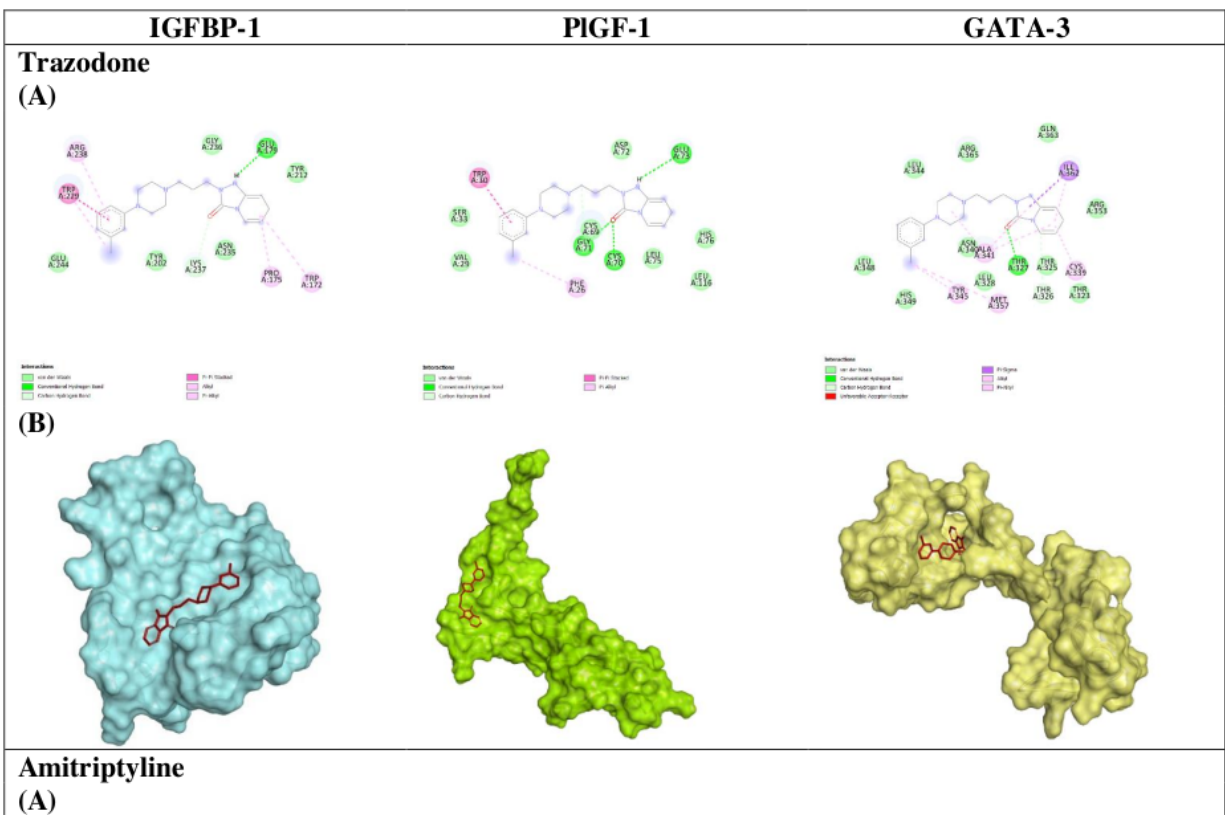
Table 1: displays the affinity values and bonds established between drugs and the IGFBP-1 protein.

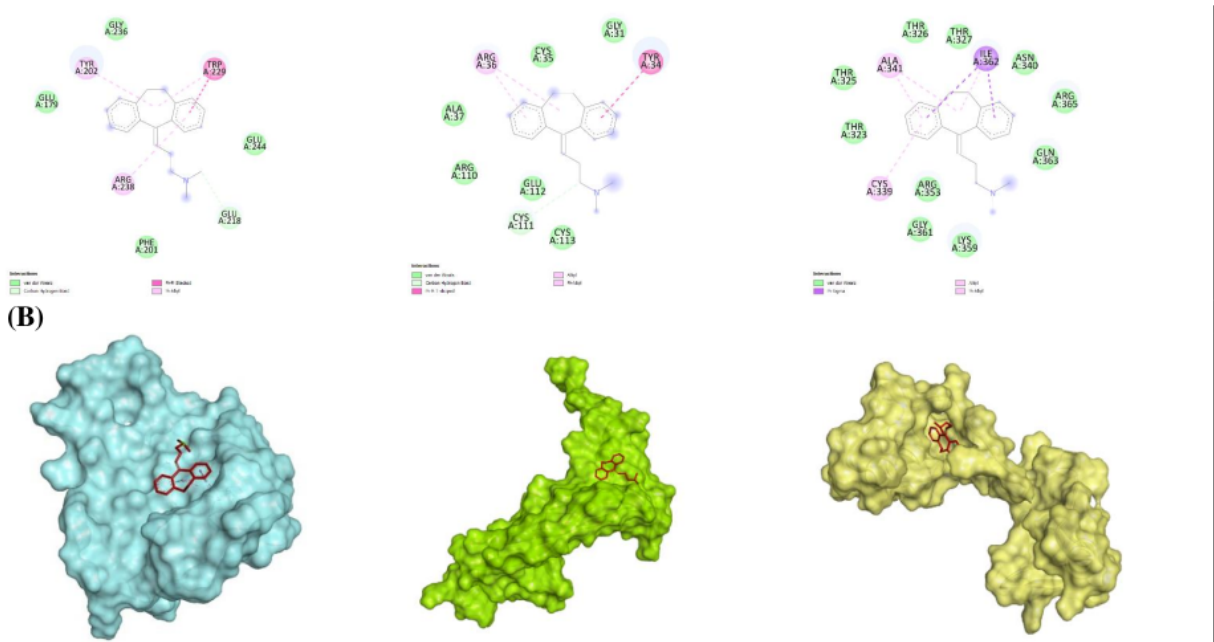
NO.	Drug	affinity (Kcal/mol)	Conventional H bond	others H bond	Number of residues implicated in interaction
1.	Trazodone	-6.80	GLU:179	LYS:237	7
2.	Amitriptyline	-6.80	TYR:202	GLU:179	5
3.	Nortriptyline	-6.80	-	GLU:218	5
4.	Mirtazapine	-6.30	-	GLY:236	4
5.	Fluoxetine	-6.00	ASN:235	GLY:236	7
6.	Duloxetine	-5.70	-	GLU:179	6
7.	Sertraline	-5.60	-	GLU:244	7
8.	Desvenlafaxine	-5.40	ARG:238	-	3
9.	Phenelzine	-5.10	TYR:202, GLY:236	-	4
10.	Tranylcypromine	-4.50	GLY:236	-	3
Average		-5.90			5.1

Table 2: displays the affinity values and bonds established between drugs and the PIGF-1 protein.

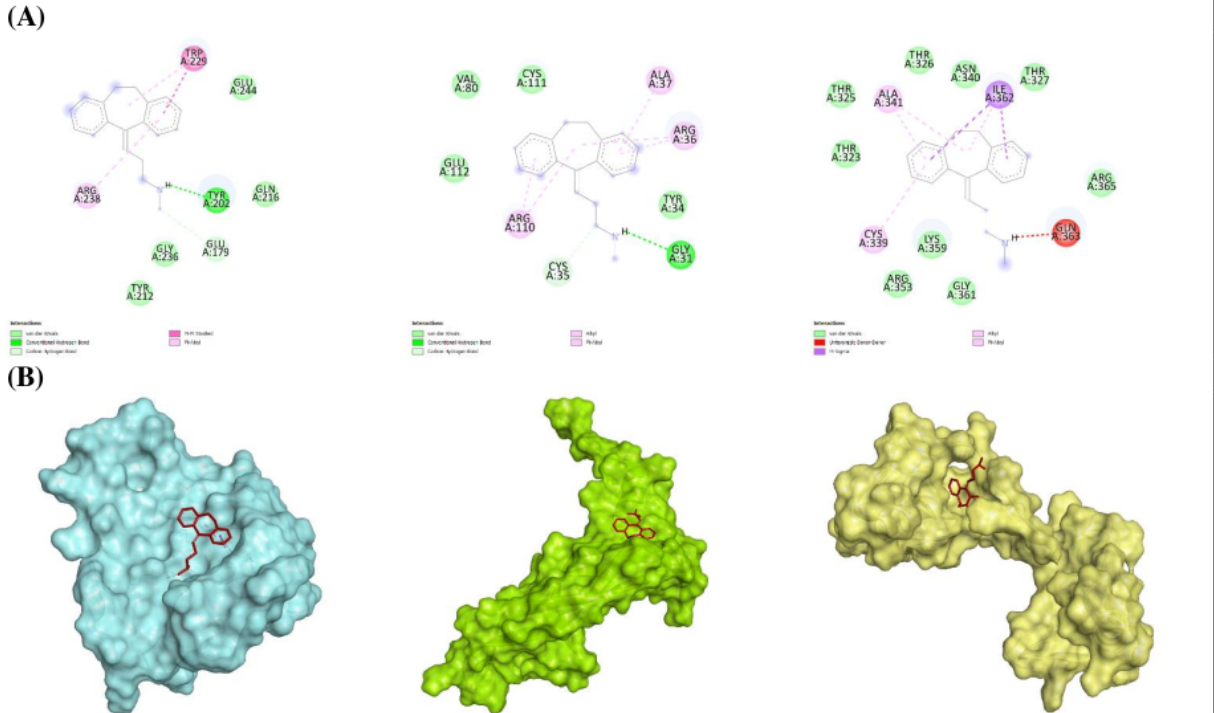
NO.	Drug	affinity (Kcal/mol)	Conventional H bond	others H bond	Number of residues implicated in interaction
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1.	Trazodone	-6.00	CYS:70, GLY:71, GLU:73	GLY:71	6
2.	Nortriptyline	-5.70	GLY:31	CYS:35	7
3.	Mirtazapine	-5.50	-	TRP:30	3
4.	Amitriptyline	-5.50	-	CYS:111	4
5.	Sertraline	-5.50	CYS:35	-	3
6.	Fluoxetine	-5.00	CYS:113	GLY:31	8
7.	Duloxetine	-4.90	CYS:70	-	4
8.	Desvenlafaxine	-4.60	CYS:113	CYS:35	8
9.	Tranlycypromine	-4.30	-	CYS:69	2
10.	Phenelzine	-3.90	-	CYS:69	2
Average		-5.90			4.7



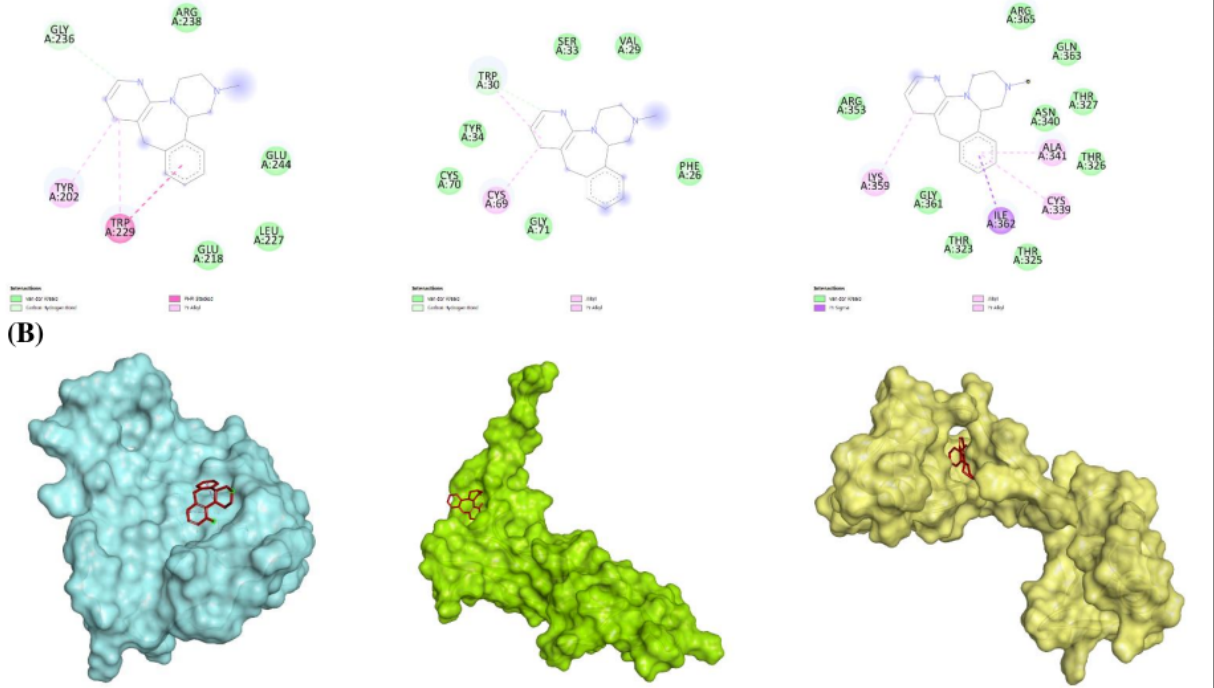


Nortriptyline

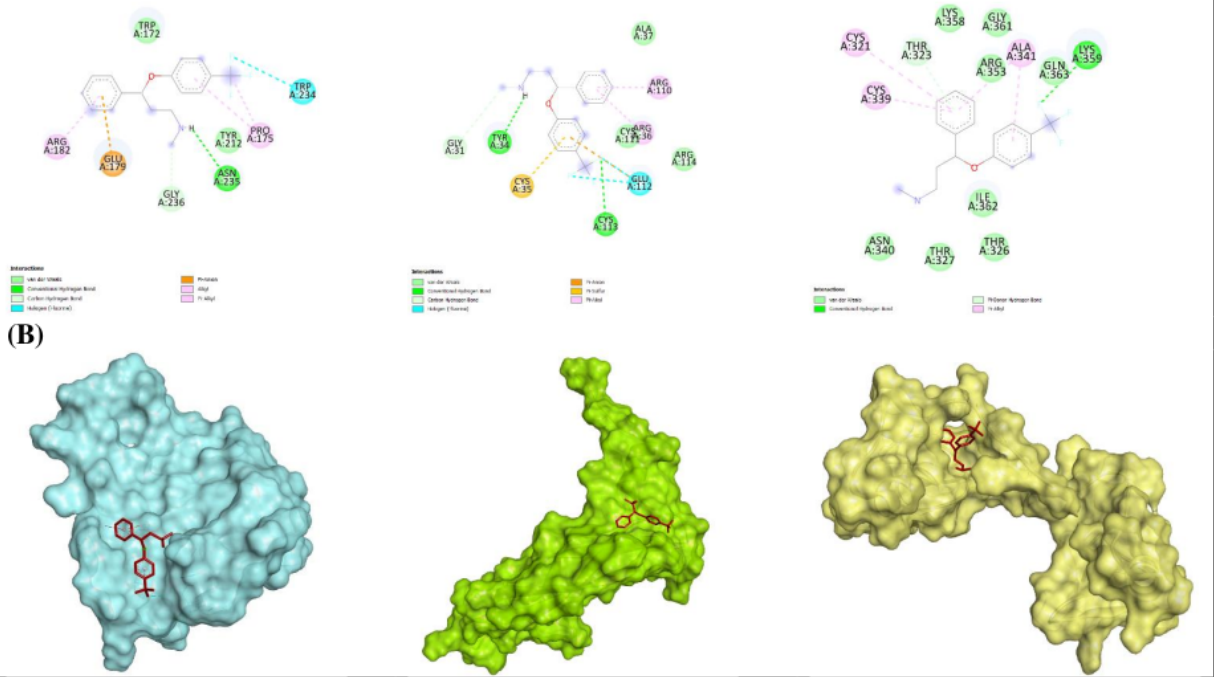


Mirtazapine

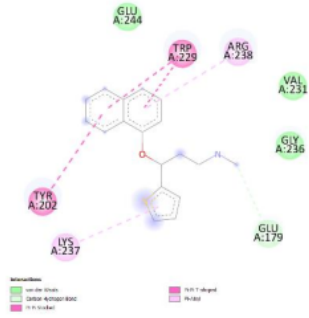




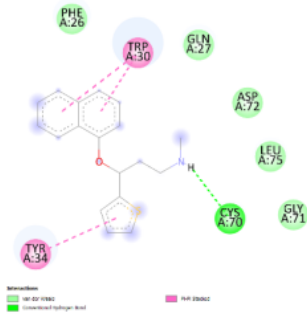
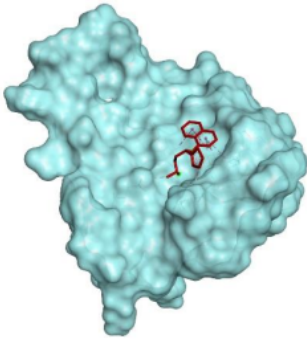
Fluoxetine
(A)



Duloxetine
(A)

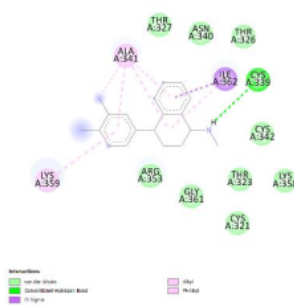
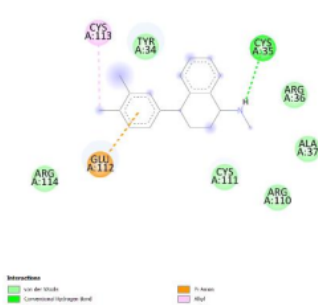
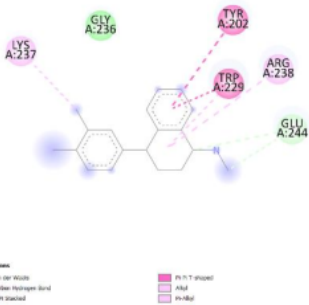


(B)

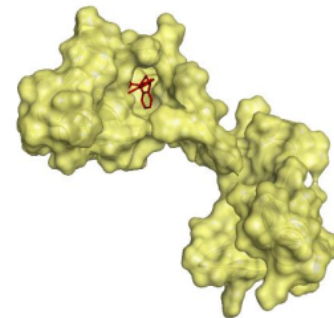
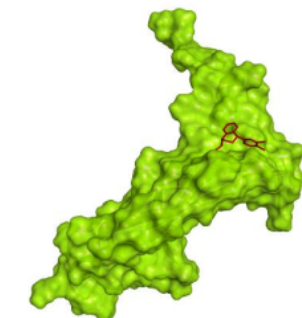
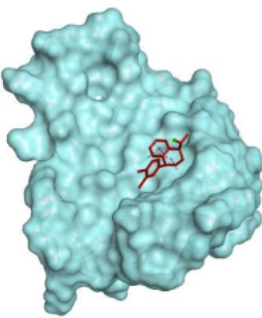


Sertraline

(A)

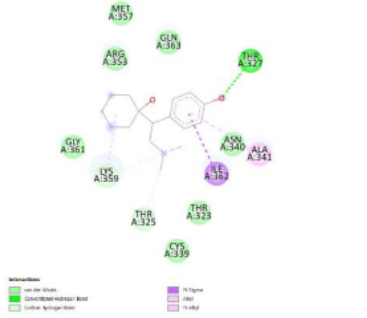
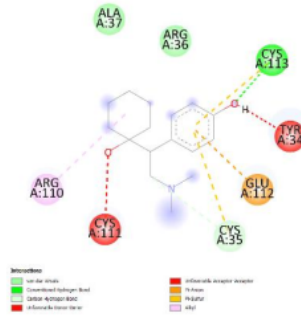
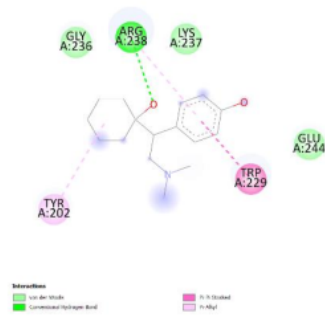


(B)

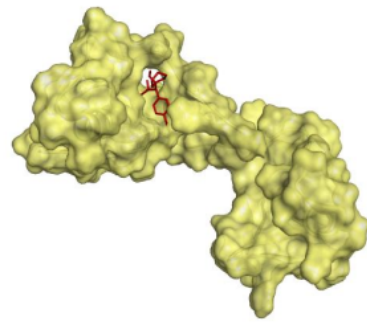
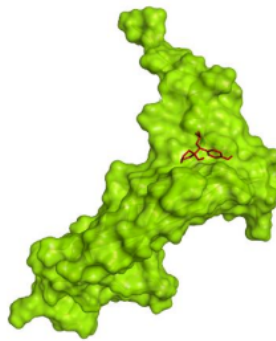
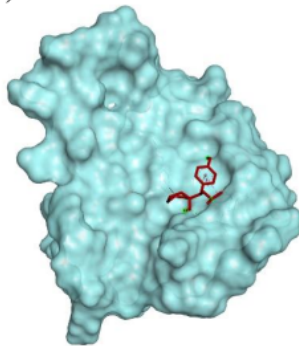


Desvenlafaxine

(A)

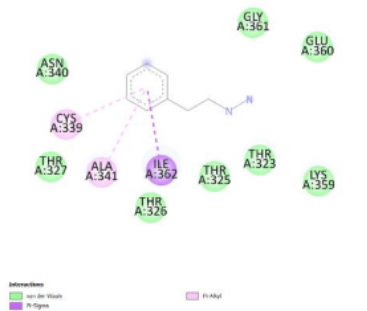
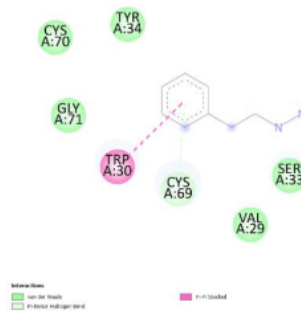


(B)

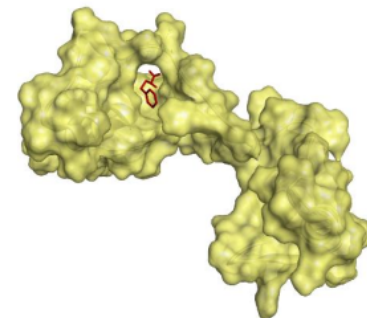
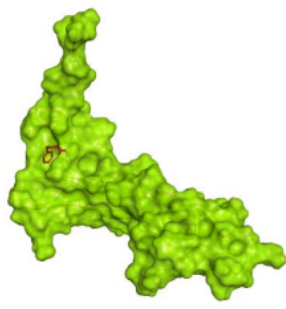
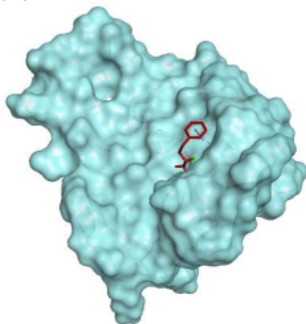


Phenelzine

(A)



(B)



Tranlycypromine

(A)

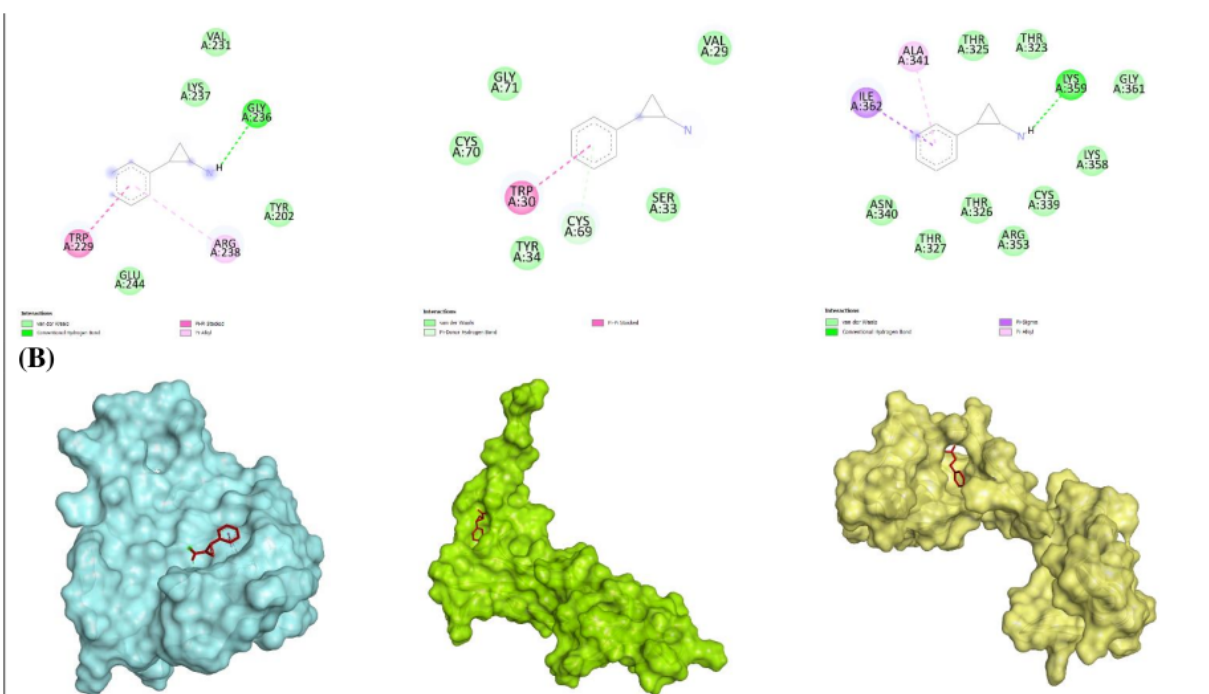


Figure 2: (A) illustrates the 2D interactions, while Figure 2(B) depicts the binding mode between drugs and proteins.

The findings from molecular docking investigations into the interactions between antidepressant drugs and human placental proteins revealed a clear inclination of all drugs to bind with the three specific proteins—IGFBP-1, PlGF-1, and GATA3—albeit with varying degrees of affinity. The affinity values for IGFBP-1 ranged between (-6.80 to -4.50) with an average of (-5.90) kcal/mol, as depicted in Table 1. Similarly, the affinity range for PlGF-1 was (-6.00 to -3.90) with an average of (-5.90) kcal/mol, as outlined in Table 2. Remarkably, the affinity range for GATA3 protein surpassed that of its counterparts, spanning between (-7.80 to -5.10) with an average of (-6.71) kcal/mol (Table 3).

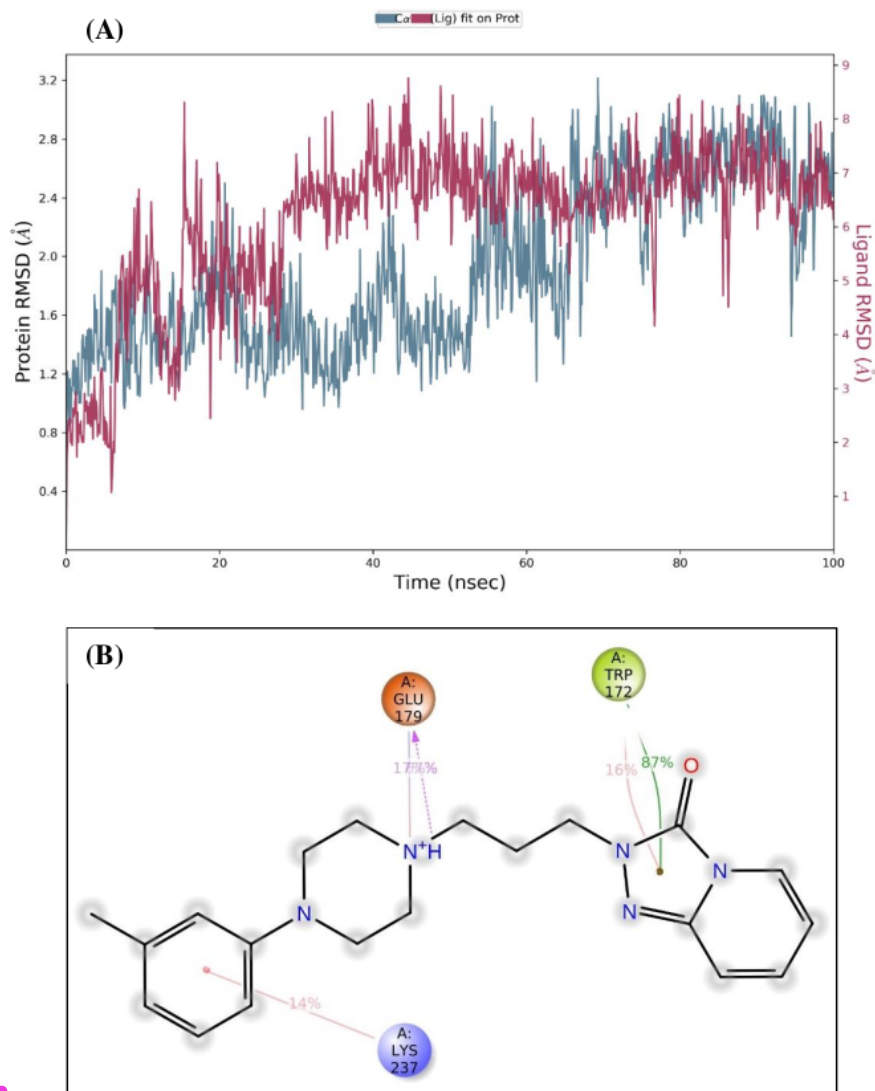
Table 3: displays the affinity values and bonds established between drugs and the GATA-3 protein.

NO.	Drug	affinity (Kcal/mol)	Conventional H bond	others H bond	Number of residues implicated in interaction
1.	Trazodone	-7.80	THR:327	THR:326	10
2.	Nortriptyline	-7.80	-	-	7
3.	Mirtazapine	-7.70	-	-	4

4.	Amitriptyline	-7.60	-	-	6
5.	Sertraline	-7.30	CYS:339	-	8
6.	Fluoxetine	-6.40	LYS:359	-	6
7.	Duloxetine	-6.20	-	-	9
8.	Desvenlafaxine	-5.90	THR:327	THR:325, LYS:359	6
9.	Phenelzine	-5.30	-	-	3
10.	Tranlycypromine	-5.10	LYS:359	-	3
Average		-6.71			6.2

Molecular Dynamic Simulation

Dynamic simulations were conducted for Trazodone, Amitriptyline, Nortriptyline, and Mirtazapine, which exhibited the highest affinity for IGF1P-1, PIGF-1, and GATA3 proteins. The findings revealed that these drugs did not attain stability with the proteins throughout the simulation period, as indicated by a Root Mean Square Deviation (RMSD) exceeding 5 Å. However, Trazodone demonstrated relatively greater stability with the IGF1P-1 protein, with its RMSD value remaining within acceptable limits (around 3 Å) (Figure 3).



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Figure3: (A) The Root Mean Square Deviation (RMSD) in angstroms (Å) of the IGFBP-1 protein with Trazodone was monitored throughout a 100 ns molecular dynamics (MD) trajectory. Both the ligand (Trazodone) and the receptor (IGFBP-1 protein) exhibited fluctuations within an acceptable range. Specifically, the IGFBP-1 protein, represented in green, displayed fluctuations within 2.5 Å, indicating stability towards the end of the simulation. Similarly, Trazodone, represented in maroon, showed relatively minor fluctuations in its binding to the protein and within its binding pocket, suggesting a stable confirmation throughout the simulation. (B) Results of 100 ns all-atom MD simulation of interactions docking poses with Trazodone.

Discussion

The intricate relationship among ¹⁵maternal depression, antidepressant use during pregnancy, and their potential impact on placental proteins is central to our investigation. Let's explore the nuanced implications of our findings, connecting them to maternal health and fetal development. The prevalence of depression during pregnancy is well-established [1-3]. ²antepartum anxiety and depression exert distinct and cumulative negative effects on both maternal and fetal well-being, the use of antidepressant medications becomes a crucial aspect of maternal care [4-7]. Our study focuses on placental proteins IGFBP-1, PIGF-1, and GATA3 due to their integral roles in embryonic development [18-22]. The Docking analysis reveals a clear inclination of antidepressant drugs to bind with these proteins, indicating potential molecular interactions that could influence crucial processes in embryogenesis. Our finding exhibited varying degrees of affinity among antidepressant drugs and placental proteins. Understanding these affinity patterns is crucial for assessing the specificity of drug-protein interactions [26]. Trazodone, Amitriptyline, Nortriptyline, and Mirtazapine exhibit high affinities for IGFBP-1, PIGF-1, and GATA3 proteins. Conversely, Desvenlafaxine, Phenelzine, and Tranylcypromine show low affinities. Due to the complexity of molecular systems, which typically comprise numerous particles, analytical determination of their properties is impractical. Molecular dynamics simulations offer a solution to this challenge through computational methods [27]. Therefore, molecular dynamics simulations were conducted for proteins exhibiting the highest binding affinity. Despite exhibiting high binding affinity with placental proteins, as indicated by the molecular docking results, the simulation findings suggest that these drugs do not establish stable interactions with placental proteins, except for Trazodone. Recognizing the importance of pregnant women taking antidepressants to protect both themselves and their fetuses [3,8-9], our findings contribute to the ongoing discourse on the careful selection of appropriate medication. Clinicians should consider these molecular insights in their decision-making process, balancing the benefits of antidepressant use with potential impacts on placental proteins and, consequently, fetal development. Future research and clinical guidelines should explore the nuanced interplay between antidepressant affinities and maternal-fetal health outcomes for a more informed approach to perinatal mental health care [28]. The findings from this study suggest that the majority of the antidepressants examined did not significantly impact the functionality of the studied placental proteins, as they failed to establish a stable binding to the functional sites of these proteins throughout the simulation period. However, Trazodone demonstrated stability within acceptable limits with the IGFBP-1 protein. This observation raises concerns about Trazodone's potential negative effect

on the protein and, consequently, its function during fetal development, which could contribute to the occurrence of congenital malformations [29].

Conclusion

In conclusion, this employing advanced computational analysis, sheds light on the complex interplay between antidepressant medications and crucial placental proteins. Choosing the safest medications, considering both mental health and the potential molecular influences of antidepressant use during pregnancy, is paramount.

Disclosure

None

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