The multi-targeted and therapeutic effect of Solasodine in menopausal syndrome

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Abstract

In-silico docking analysis has emerged as a powerful tool for predicting the multi-targeted therapeutic effects of bioactive compounds. In this study, we aimed to investigate the potential multi-targeted therapeutic effect of Solasodine, a natural compound, in menopausal syndrome. Specifically, we focused on its interaction with four key targets involved in menopausal syndrome: TNF Alpha, Caspase-3 (CASP-3), Catalase (CAT), and Estrogen Receptor (ER). Using molecular docking simulations, we evaluated the binding affinity and interactions of Solasodine with these target proteins. The results revealed favorable binding energies and strong interactions between Solasodine and the target proteins, suggesting a potential therapeutic effect of Solasodine on menopausal syndrome through multi-targeted modulation. Docking analysis of Solasodine with TNF Alpha, a pro-inflammatory cytokine implicated in menopausal symptoms, demonstrated a high binding affinity, indicating its potential as an anti-inflammatory agent. Furthermore, Solasodine exhibited strong interactions with CASP-3, a key protein involved in apoptosis, suggesting its potential role in regulating cell death pathways associated with menopausal syndrome. Additionally, Solasodine demonstrated significant binding to CAT, an enzyme involved in oxidative stress regulation. This suggests that Solasodine may possess antioxidant properties, potentially alleviating oxidative stress-related symptoms experienced during menopause. Lastly, the docking analysis revealed interactions between Solasodine and ER, suggesting its potential estrogenic effects, which could be beneficial for hormone-related symptoms in menopausal women. Overall, the in-silico docking analysis highlights the multi-targeted therapeutic potential of Solasodine in menopausal syndrome by interacting with TNF Alpha, CASP-3, CAT, and ER. These findings provide valuable insights into the molecular

mechanisms underlying Solasodine's therapeutic effects, supporting further experimental studies to validate its efficacy in menopausal syndrome.

Keywords: Solasodine, Menopausal syndrome, TNF Alpha, Caspase-3 (CASP-3), Catalase (CAT), and Estrogen Receptor (ER)

Introduction

Menopausal syndrome, also known as menopause or climacteric, refers to the physiological and psychological changes experienced by women as they transition from their reproductive years to post-menopause. The pathophysiology of menopausal syndrome primarily involves hormonal changes, particularly a decline in estrogen levels, which leads to various symptoms and long-term health effects [1]. During menopause, the ovaries gradually decrease their production of estrogen and progesterone. This decline in hormonal levels disrupts the delicate balance that regulates the menstrual cycle and affects the functioning of multiple organ systems. Estrogen deficiency affects the hypothalamic-pituitary-ovarian axis, leading to irregular menstrual cycles and eventually cessation of menstruation. The hormonal fluctuations and subsequent estrogen deficiency give rise to a wide range of symptoms, including hot flashes, night sweats, vaginal dryness, mood swings, sleep disturbances, cognitive changes, and urogenital atrophy [2,3]. Additionally, estrogen plays a crucial role in maintaining bone density, and its decline during menopause increases the risk of osteoporosis and fractures. The epidemiology of menopausal syndrome varies across different populations. The average age of menopause onset is around 51 years, but it can occur earlier or later depending on various factors such as genetics, ethnicity, lifestyle, and overall health. Certain populations, such as smokers and those with a family history of early menopause, may experience menopause at a younger age [4].

The menopausal syndrome affects nearly all women to some extent, with varying severity of symptoms. However, the frequency and intensity of symptoms can vary significantly among individuals. The duration of menopausal symptoms also varies, with some women experiencing them for a few months to a couple of years, while others may have persistent symptoms for a longer period. Although it has been considered that menopause is a natural physiological process, not a disease. However, the symptoms associated with menopausal syndrome can significantly impact a woman's quality of life. Understanding the pathophysiology and epidemiology of menopausal syndrome helps healthcare professionals provide appropriate management strategies and support to women experiencing these changes, ensuring a smoother transition and improved overall well-being [1,5].

Medicinal plants, also known as medicinal herbs or herbal medicines, have been used for centuries as natural remedies to promote health and treat various ailments [6–8]. These plants contain bioactive compounds, such as alkaloids, flavonoids, terpenoids, and phenolic compounds, which possess therapeutic properties [9–11]. The use of medicinal plants can be traced back to ancient civilizations, where traditional healers and herbalists relied on their knowledge of plants and their medicinal properties to treat illnesses. Over time, this traditional knowledge has been passed down through generations and has been integrated into various systems of traditional medicine, such as Traditional Chinese Medicine (TCM), Ayurveda, and Native American herbal medicine [12,13].

Medicinal plants offer a wide range of health benefits and have been used to alleviate symptoms, support the immune system, improve digestion, promote relaxation, and address various health conditions [14–17]. Common examples of medicinal plants include aloe vera, ginger, ginseng, turmeric, echinacea, chamomile, and garlic, among many others. In recent years, there has been a resurgence of interest in medicinal plants as people seek natural alternatives to conventional medicine. Scientific research has focused on validating the traditional use of these plants, exploring their active compounds, and understanding their mechanisms of action. This research has led to the development of herbal supplements, phytochemical-based drugs, and the incorporation of herbal medicine into complementary and alternative medicine practices [12,16,18,19].

However, it is important to note that while medicinal plants offer potential therapeutic benefits, their use should be approached with caution. Proper identification, quality control, and standardized manufacturing processes are essential to ensure the safety and efficacy of herbal products. Additionally, it is advisable to consult with healthcare professionals or qualified herbalists to ensure appropriate usage and minimize any potential interactions or adverse effects [20,21].

Solasodine is a naturally occurring steroidal alkaloid found in various plants, including the Solanaceae family. This compound has gained significant attention due to its potential medicinal properties and diverse applications in the pharmaceutical industry. Solasodine has been studied for its anti-inflammatory, anticancer, antifungal, and antiviral activities. It exhibits cytotoxic effects on cancer cells, making it a promising candidate for cancer treatment. Solasodine has been investigated for its potential to inhibit the growth and proliferation of various cancer types, including breast, lung, colon, and prostate cancers. Furthermore, solasodine has been explored for its anti-inflammatory effects. It inhibits the production of pro-inflammatory cytokines and enzymes, potentially providing therapeutic benefits for inflammatory conditions [22,23]. While it shows promise in various areas, further studies are necessary to fully understand its mechanisms of action and therapeutic targets of solasodien for menopausal syndrome.

1. Methodology

1.1. Requirements of the software

To perform this study, Autodock (Version: 1.5.7) (20), and Discovery Studio tools (Version: 2021 client) (20) were used to determine the multi-mechanistic and therapeutic action of the drug.

1.2. In-silico docking analysis

To explore potential molecular targets of proteins in ligand-protein interactions, an analysis was conducted. The Autodock tool was utilized to investigate the impact of Solasodine on four proteins: TNF Alpha (PID: GRMJ), Caspase-3 (CASP-3, PID: 3GJQ), Catalase (CAT, PID: 1QQW), and Estrogen Receptor (ER, PID: 1A52). The protein structures were obtained from the RCSB protein data bank, while the 3D ligand of Rosmarinic Acid was retrieved from the PubChem database. The main objective of this study was to assess the binding affinity and potential therapeutic interactions between Solasodine and the target proteins, employing in-silico docking analysis. By utilizing molecular docking simulations, valuable insights into the multi-targeted therapeutic effects of Solasodine in relation to various molecular pathways associated with the menopausal syndrome were sought [19].

To create a ligand for this analysis, the drug discovery studio visualizer program (Version: 2021 client) was used to convert the SDF file to PDB format. It was then constructed for docking analysis with protein and converted to PDBQT format. In order to charge the protein and characterize its interaction with the ligand, heat atoms have been eliminated from the protein geometry throughout the study. Hydrogen atoms were then added. The bodies of both humans and animals include charged macromolecules that are atom-complete. Therefore, before continuing with the docking experiment, it is necessary and appropriate to add charges and missing atoms (hydrogen and, in certain cases, non-hydrogen) to proteins, regardless of the docking tool/software and methodology used. The Kcol/mol unit, which is used to measure a molecule's energy, was used to express the binding energy between the ligand and protein [24,25].

2. Results and discussion

2.1. In-silico docking analysis

In-silico docking analysis of solasodine was performed on different proteins to determine the multi-targeted and therapeutic action in amelioration of menopausal syndrome. TNF-alpha is a cytokine involved in the regulation of inflammation and immune responses. During menopause, there may be changes in the levels of pro-inflammatory cytokines like TNF-alpha, which can contribute to symptoms such as hot flashes and mood changes. It is believed that reducing inflammation and modulating TNF-alpha levels may help alleviate these symptoms. However, the specific effects of solasodine on TNF-alpha have not been extensively studied in the context of menopausal syndrome. TNF-alpha is a pro-inflammatory cytokine that plays a role in the immune response and inflammation. During menopause, there can be alterations in the balance of inflammatory factors like TNF-alpha, which may contribute to symptoms such as hot flashes, mood changes, and other inflammatory conditions. The results of the study reveled that solasodine significantly interact with the proteins such as TNF, CAT, CASP-3, etc. The interaction profile of solasodine with CAT has been summarized in figure 1.

(A) (B)

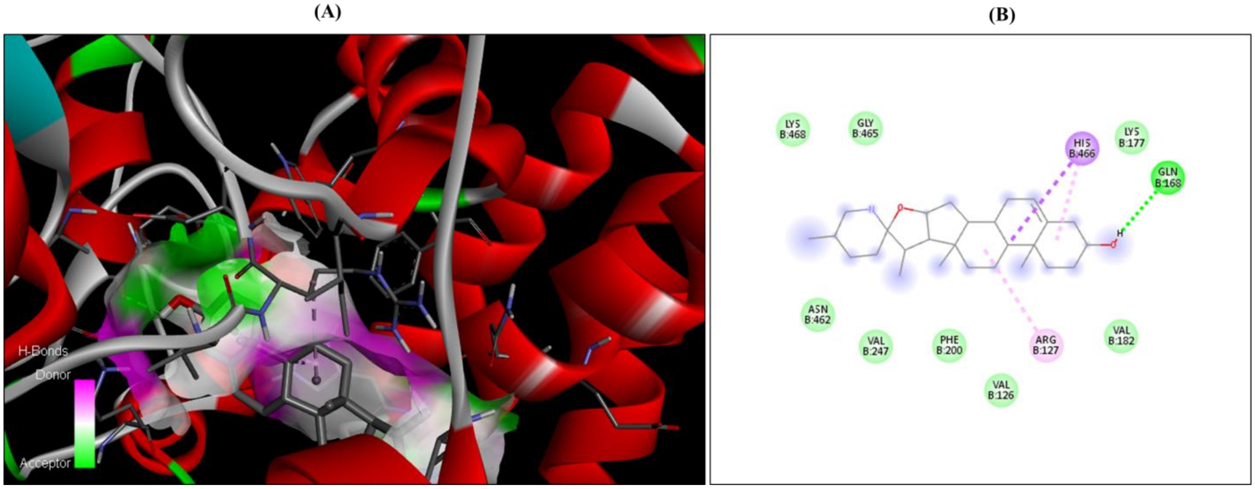

Figure 1: In-silico docking profiling of solasodine with CAT. Figure (A) represents 3D protein and ligand interaction while Figure (B) represents 2D interaction of solasodine with CAT protein.

While solasodine is a steroidal alkaloid found in certain plants and has been studied for its potential therapeutic effects, there is limited information available on its direct effects on TNF-alpha levels or activity in menopausal syndrome. That being said, some studies have suggested that natural compounds with anti-inflammatory properties may have the potential to modulate TNF-alpha levels and activity. Solasodine and other natural compounds may exhibit anti-inflammatory properties through various mechanisms, such as inhibiting inflammatory pathways or reducing the production of pro-inflammatory cytokines. To understand the specific effects of solasodine on TNF-alpha in menopausal syndrome, further scientific research is needed. It's important to consult with a healthcare professional or medical expert for personalized advice and guidance regarding the use of solasodine or any other supplements or treatments for managing menopausal symptoms, including inflammation. Natural compounds may interfere with specific signaling pathways involved in inflammation, such as the nuclear factor-kappa B (NF-kB) pathway. NF-kB is a transcription factor that plays a key role in the production of pro-inflammatory cytokines like TNF-alpha. Natural compounds may exert inhibitory effects on NF-kB, thereby reducing TNF-alpha production [9,10], [1,2].

Some natural compounds possess antioxidant properties, which can help mitigate inflammation. Oxidative stress can promote the production of pro-inflammatory cytokines like TNF-alpha. By scavenging reactive oxygen species (ROS) and reducing oxidative stress, natural compounds may indirectly modulate TNF-alpha levels. Natural compounds can potentially affect gene expression related to inflammation and cytokine production. By targeting specific genes involved in TNF-alpha synthesis or regulation, these compounds may influence TNF-alpha levels as well as impact the activity and function of immune cells, including those involved in inflammation. By modulating immune cell responses, these compounds may indirectly influence TNF-alpha production [26].

Catalase (CAT) is an antioxidant enzyme that plays a crucial role in neutralizing reactive oxygen species (ROS) and protecting cells from oxidative stress. Oxidative stress can occur during menopause due to the decline in estrogen levels, leading to symptoms such as fatigue and cognitive changes. Enhancing antioxidant defense mechanisms, such as the activity of CAT, may help mitigate oxidative stress-related symptoms. CAT is an enzyme that plays a crucial role in the antioxidant defense system of cells. It helps to break down hydrogen peroxide, a reactive oxygen species (ROS), into water and oxygen, thus protecting cells from oxidative damage. During menopause, there can be an increase in oxidative stress due to the decline in estrogen levels. Oxidative stress has been associated with various symptoms experienced during menopause, such as hot flashes, mood changes, and cognitive disturbances [27], [10].

While solasodine is a steroidal alkaloid found in certain plants and has been studied for its potential therapeutic effects, I could not find specific studies investigating its direct effects on CAT activity in the context of menopause. Therefore, it is unclear how solasodine may influence CAT levels or activity in menopausal syndrome. To understand the potential effects of solasodine on CAT activity in menopausal syndrome, further scientific research is needed. It's always advisable to consult with a healthcare professional or medical expert for personalized advice and guidance regarding the use of solasodine or any other supplements or treatments for managing menopausal symptoms. The interaction profile of solasodine with TNF-α has been summrised in figure 2.

(A) **(B)**

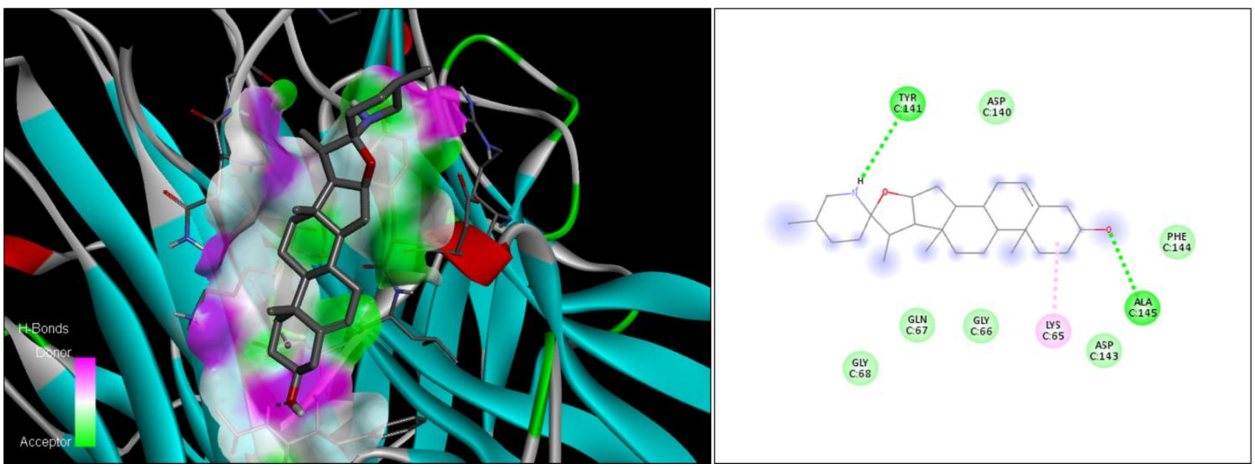

Figure 2: In-silico docking profiling of solasodine with TNF-α. Figure (A) represents 3D protein and ligand interaction while Figure (B) represents 2D interaction of solasodine with TNF-α protein.

Caspase-3 (CASP-3) is an enzyme involved in apoptosis, the programmed cell death process. Estrogen plays a role in regulating apoptosis, and its decline during menopause can affect various tissues. Imbalances in apoptosis can contribute to symptoms such as vaginal dryness and tissue changes. Modulating CASP-3 activity may help maintain the balance between cell survival and apoptosis. However, the specific effects of solasodine on CASP-3 in menopausal syndrome have not been well-studied [8]. In this study, the interaction of solasodine has been determined with the CASP-3 protein and found significantly active and the outcomes are summrised in figure 3.

(A) (B)

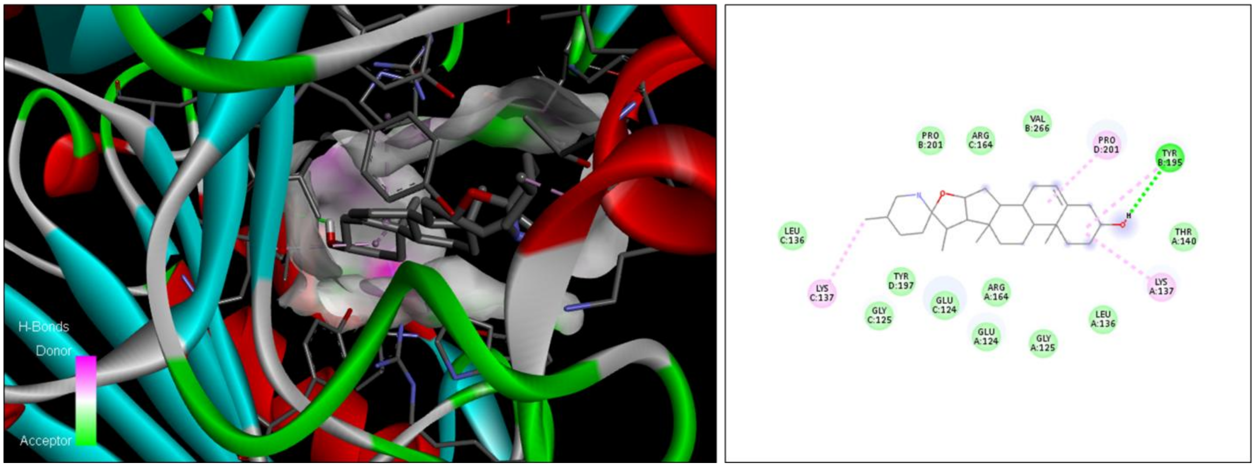

Figure 3: In-silico docking profiling of solasodine with CASP-3. Figure (A) represents 3D protein and ligand interaction while Figure (B) represents 2D interaction of solasodine with CASP-3 protein.

Estrogen is a hormone that plays a vital role in various physiological processes, including the regulation of body temperature, mood, sleep, and vaginal health. During menopause, estrogen levels decline, leading to hormonal imbalances and associated symptoms. Hormone replacement therapy (HRT) is a common approach to managing menopausal symptoms by supplementing estrogen levels. However, solasodine's effects on estrogen levels have not been widely investigated. It primarily produced by the ovaries, and its levels decline during menopause. The hypothalamus and pituitary gland in the brain release hormones (GnRH, FSH, and LH) that stimulate the ovaries to produce estrogen. However, during menopause, the number of ovarian follicles decreases, leading to reduced estrogen production. Estrogen levels are also influenced by feedback mechanisms involving the hypothalamus, pituitary gland, and the ovaries. Progesterone is primarily produced by the ovaries following ovulation. During menopause, as ovulation becomes less frequent, progesterone production decreases. The hypothalamus and pituitary gland release hormones (GnRH, FSH, and LH) to stimulate progesterone production in the ovaries [28,29]. Similar to estrogen, progesterone levels are regulated by feedback mechanisms involving the hypothalamus, pituitary gland, and the ovaries. The biomolecular regulation of estrogen and progesterone levels during menopause involves intricate interactions between the hypothalamus, pituitary gland, and the ovaries. Hormonal feedback mechanisms play a crucial role in maintaining the balance of these hormones. Furthermore, the interaction profile of ER has been summrised in Figure 4.

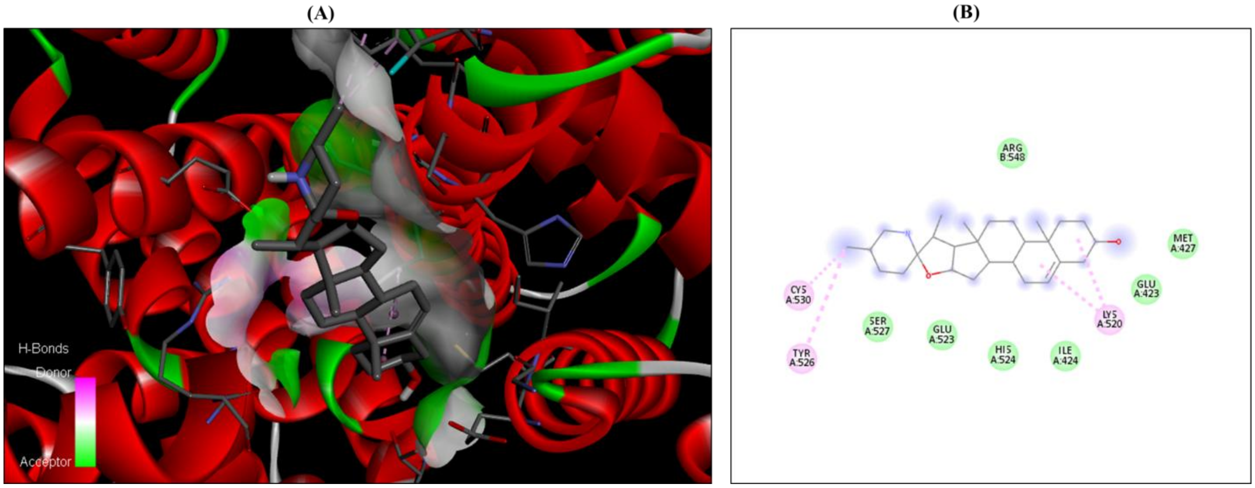

Figure 4: In-silico docking profiling of solasodine with CASP-3. Figure (A) represents 3D protein and ligand interaction while Figure (B) represents 2D interaction of solasodine with CASP-3 protein.

Regarding the specific effects of solasodine on estrogen and progesterone levels in menopausal syndrome, there is limited scientific research available. Therefore, the understanding of the biomolecular mechanisms through which solasodine may influence estrogen and progesterone levels in menopause is still unclear. While solasodine is a steroidal alkaloid found in certain plants and has been studied for its potential therapeutic effects, its specific estrogenic activity has not been extensively investigated [30,31]. Furthermore, the docking outcomes of each protein have been defined in the figure 5.

CAT

Refining results ... done.

mode	affinity (kcal/mol)	dist from best mode rmsd l.b.	rmsd u.b.
1	-8.9	0.000	0.000
2	-8.9	1.727	2.863
3	-8.6	67.888	74.100
4	-8.6	19.497	22.136
5	-8.5	21.163	22.206
6	-8.3	23.395	24.955
7	-8.2	15.715	17.638
8	-8.2	30.381	32.916
9	-8.1	42.077	46.436

TNF-α

mode	**affinity (kcal/mol)**	**dist from best mode rmsd l.b.**	**rmsd u.b.**
1	**-7.4**	**0.000**	**0.000**
2	**-7.4**	**1.775**	**2.829**
3	**-7.3**	**32.137**	**34.383**
4	**-7.3**	**3.230**	**5.799**
5	**-7.3**	**33.156**	**35.969**
6	**-7.1**	**17.783**	**19.447**
7	**-7.0**	**45.719**	**48.211**
8	**-6.9**	**5.649**	**8.465**
9	**-6.7**	**16.866**	**18.721**

CASP-3

mode	affinity (kcal/mol)	dist from best mode rmsd l.b.	rmsd u.b.
1	-10.3	0.000	0.000
2	-10.2	2.400	9.212
3	-10.0	2.708	9.206
4	-9.6	1.672	3.335
5	-8.9	2.936	4.477
6	-8.6	2.951	4.541
7	-8.5	2.116	3.184
8	-8.4	4.788	6.990
9	-8.4	2.947	9.038

ER

mode	affinity (kcal/mol)	dist from best mode rmsd l.b.	rmsd u.b.
1	-8.0	0.000	0.000
2	-8.0	13.588	15.998
3	-8.0	9.869	12.707
4	-7.9	4.607	8.333
5	-7.9	3.542	5.829
6	-7.8	15.127	17.890
7	-7.8	32.031	34.991
8	-7.7	27.694	30.631
9	-7.7	41.413	43.711

Figure 5: In-silico interaction profile and binding energy of solasodine with the proteins such as CAT, TNF, CASP-3 and ER.

It's worth noting that steroidal alkaloids, in general, can have diverse effects on hormonal regulation due to their structural similarity to steroids. However, the specific estrogenic activity of solasodine and its potential impact on menopausal symptoms or hormonal balance remain to be determined. The outcome scientific information and help determine the most appropriate approaches for managing menopausal symptoms.

3. Conclusion

In conclusion, the in-silico docking analysis conducted in this study provided valuable insights into the multi-targeted therapeutic effects of Solasodine in menopausal syndrome. Through its interactions with TNF Alpha, Caspase-3, Catalase, and Estrogen Receptor proteins, Solasodine demonstrated potential as a promising therapeutic agent. The docking analysis revealed favorable binding affinities and strong interactions between Solasodine and the target proteins. These findings suggest that Solasodine may exert anti-inflammatory effects by modulating TNF Alpha, regulate apoptosis pathways through Caspase-3, alleviate oxidative stress-related symptoms by targeting Catalase, and potentially exert estrogenic effects through interaction with Estrogen Receptor. By targeting multiple molecular pathways involved in menopausal syndrome, Solasodine holds promise as a multi-targeted therapeutic agent. However, further experimental studies are warranted to validate its efficacy and elucidate the underlying mechanisms in vivo. The results of this in-silico docking analysis provide a foundation for future research and the development of novel interventions for menopausal syndrome. Solasodine emerges as a potential candidate for further exploration as a natural compound with multi-targeted therapeutic effects in alleviating the symptoms associated with menopause.

Conflict of interest

All authors declare no conflict of interest.

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