chemistry proceedings

MDPI

Proceeding Paper

Studies on Anti-Cancer Agents from Natural Resources with Special Reference to *Cannabis sativa* & *Datura metel* L. †

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† Presented at The 28th International Electronic Conference on Synthetic Organic Chemistry (ECSOC 2024), 15–30 November 2024; Available online: https://sciforum.net/event/ecsoc-28.

Abstract: Cancer remains a significant challenge, prompting exploration of new therapies. Breast cancer is the most prevalent among women, and current medications often have serious side effects. Additionally, there's limited research on natural resources that historically provided bioactive compounds with potential anti-cancer properties. This study examines two such resources: *Cannabis sativa* and *Datura metel* L., both known for their pharmacological diversity and traditional medicinal use. *Cannabis sativa*, with its major constituents Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD), has garnered considerable interest. *Datura metel* L., despite its toxicity, contains alkaloids like scopolamine and withametelin, which have shown cytotoxic properties against cancer cells. This study selected five breast cancer-related receptors, docking them against various phytoconstituents in both plants to identify potent cytotoxic entities. Target proteins were extracted from the PDB database, and docking studies were performed using AutoDock software. The docking scores of the phytochemicals were then compared with each other. The docking studies on *Cannabis sativa* revealed that apigenin (−8.15), β-caryophyllene oxide (−8.35), THCA (−8.84), epicatechin (−8.18), and vitexin (−9.58) showed good interaction with the PARP receptor (PDB ID: 5DS3), while cannabidiol (−8.38) and cannabichromene (−8.36) showed strong interactions with CDK4/6 (PDB ID: 6GS7). Additionally, strychnine (−9.99), naringin (−9.19), and luteolin (−8) demonstrated good interactions with the estrogen receptor (PDB ID: 3ERT). In the case of *Datura metel* L., withametelin (−10.69) and dinoxin B (−10.72) showed good interactions with the estrogen receptor (PDB ID: 3ERT), and scopolamine (−8.24) with CDK4/6 (PDB ID: 6GS7). These findings suggest that these phytoconstituents possess anticancer activities.

Keywords: cancer; breast cancer; anti-cancer agents; *Cannabis sativa*; *Datura metel* L.; docking

Citation: Chakraborty, S.; Kumar, P.; Ghosh, M. Studies on Anti-Cancer Agents from Natural Resources with Special Reference to *Cannabis sativa* & *Datura metel* L. *Chem. Proc.* **2024**, *6*, x. https://doi.org/10.3390/xxxxx

Academic Editor(s): Name

Published: 15 November 2024

1. Introduction

In this 21st century, the disease which is persistently leading its competitors, in spite of the therapeutical advancements is cancer. It is associated with those genes which lose their capability to control cell proliferation, metabolism, DNA repair and death, while they undergo mutational changes. Besides the cancer cell, the microenvironment enveloping it, stimulates the initiation and progression of tumors, whose growth affect the healthy cells both physically and biochemically [1]. Every year one-sixth of the global deaths are accounted by cancer, where 10 million people die while more than 19 million are diagnosed annually [2]. There are more than 30 types of cancer reported till date, amongst which breast cancer stands out to be one of the majors. According to the epidemiological data, around 2,308,897 new cases and 665,684 deaths due to female breast cancer were reported in the year 2022, ranking the same as 2nd and 4th in the rates of incidence and mortality, respectively [3]. The major determinants linked with breast cancer are female gender, older age, early menarche, late menopause, lack of breastfeeding,

genetic factors, nulliparity, hormonal status, dense breast tissue, exposure to ionizing radiation and economic development of the country [4,5].

Over the years, chemotherapy has been the predominant option for treating cancer patients, for instance Tamoxifen is one of the most commonly used medications for treating breast cancer. However, these drugs are associated with adverse effects which consequently deteriorate the patient's heath, despite ameliorating the impact of cancer. In such a situation, the unexplored arena of natural resources whose anti-cancer properties have long been reported in the Ayurveda, should be looked upon meticulously. There are several secondary metabolites like vinca alkaloids, taxane diterpenoids, etc. which can be extracted from plant sources and employed in treating cancer [6]. Amongst those natural sources, *Cannabis sativa* and *Datura metel* L. are two of the medicinal plants which are rich in phytochemicals an are potential anti-cancer agents. *Cannabis sativa*, an annual plant of Cannabaceae family is widely associated as a treatment against various medical conditions. It houses more than 150 phytocannabinoids and numerous flavonoids and terpenes, namely Δ^9-tetrahydrocannabinol (THC/THCA), cannabidiol (CBD), etc. [7]. On the other hand, *Datura metel* L., a perennial herbaceous member of Solanaceae family, contains multiple alkaloids, tannins, phenols, sterols and saponins, among which constituents like withametelin, scopolamine, etc. carry medicinal properties [8].

2. Method

2.1. Studying Molecular Docking

Molecular docking is a computational technique that is commonly used in drug discovery and design. It involves predicting the binding mode and affinity of a small molecule ligand to a protein target. This is achieved through the calculation of the energetics and geometry of the interaction between the ligand and the protein. It is a powerful tool for drug discovery and design, as it can predict the binding mode and affinity of small molecules to a protein target. This is important for understanding the mechanism of action of a drug and optimizing its efficacy and safety.

2.2. Selecting Proteins

The untoward expression of various proteins is the sole reason responsible for the unbridled proliferation of the cancer cells. Development of breast cancer is stimulated by several factors such as upregulation of IGF1R overexpression of MYC (myelocytomatosis) oncogene, activation of tyrosine kinases receptor along with EGFR1 (epidermal growth factor receptor 1) or HER2 (human epidermal growth factor receptor 1), which in turn induces signaling pathways like Ras/MAPK/ERK or PI3K/AKT/mTOR, upregulation of IGF1R (insulin like growth factor 1 receptor and lack of expression of tumor suppressor genes like BRCA1/2 (breast cancer) [9]. The PARP (Poly (ADP-ribose) polymerase) proteins when inhibited, targets the DNA damage response in BRCA1/2 mutated breast cancer [10]. Moreover, TP53 (tumor protein p53) mutation and loss of expression of PTEN (Phosphatase and Tensin homolog) diminishes their anti-proliferative nature against the cancer cells. Androgen receptor (AR) also has an active role in the stimulation and expansion of both ER (estrogen receptor) positive and negative breast cancer cells [9]. The ER-cyclin D-CDK4/6 (cyclin dependent kinases) pathway is another potential site whose inhibition can prevent ER positive breast cancer [11]. Keeping in mind such information, this study employed five receptors, namely ER (PDB IDs—3ERT, 1A52), PI3K (PDB ID—6B1O), CDK4/6 (PDB ID—6GS7), PARP (PDB ID—5DS3) and EGFR (PDB ID—1M17 to carry out the experiment.

2.3. Selecting Phytoconstituents

After screening through the phytoconstituents present in the plants concerned, the major 25 and 6 components were selected from *Cannabis sativa* and *Datura metel* L. respectively, which are enlisted in Table 1 and Table 2.

Table 1. Docking Score (List of phytoconstituent in *Cannabis sativa*).

Compound Name	CDK4/6 (PDB ID:6GS7)	EGFR (PDB ID:1M17)	Estrogen (PDB ID:3ERT)	PARP (PDB ID:5DS3)	PI3K (PDB ID:6B1O)
Apigenine	−7.09	−6.83	−8.13	−8.15	−6.61
α-Humulene	−7.16	−6.16	−7.37	−7.36	−5.75
B-Caryophyllene Oxide	−7.29	−6.73	−7.56	−8.35	−5.74
Luteolin	−7.29	−7.14	−8	−7.94	−6.42
Cannabichromene	−8.36	−7.68	−8.41	−8.26	−7.35
Cannabidiol acid	−7.94	−6.79	−7.25	−7.14	−7.02
Cannabidiol	−8.38	−7.08	−7.95	−7.48	−6.84
THCA	−8.19	−8.56	−8.17	−8.84	−6.52
Cannabigerol	−7.73	−6.94	−7.41	−7.95	−7.01
Rosmarinic acid	−6.1	−7.07	−7.47	−7.99	−3.6
P-OH—benzoic acid	−4.64	−4.56	−3.71	−4.97	−3.94
Gallic Acid	−4.94	−4.25	−4.16	−5.34	−4.35
Ferulic Acid	−4.73	−6.05	−4.7	−5.94	−4.46
Linalool	−4.93	−4.87	−5.75	−5.5	−4.95
Epicatechin	−7.41	−7.41	−7.54	−8.18	−6.15
Catechin	−7.4	−7.44	−7.54	−7.91	−7.09
Naringin	−8.17	−8.54	−9.19	−8.1	−7.34
Naringenin	−6.56	−6.39	−7.51	−7.39	−6.31
α-pinene	−5.24	−4.86	−5.78	−6.13	−5.22
B-myrcene	−4.54	−4.34	−4.57	−5.27	−4.19
Caryophyllene	−6.97	−6.78	−7.65	−7.62	−5.54
Vitexin	−6.88	−7.22	−7.21	−9.58	−5.01
Myrcene	−4.52	−4.35	−4.57	−5.3	−4.25
Combretastatin	−7.6	−6.83	−6.34	−7.59	−6.08
Strychnine	−8.93	−8.95	−9.99	−9.73	−8.73

Table 2. Docking Score (List of phytoconstituent in *Datura metel* L.).

Compound Name	CDK4/6 (PDB ID:6GS7)	EGFR (PDB ID:1M17)	Estrogen (PDB ID:3ERT)	PARP (PDB ID:5DS3)	PI3K (PDB ID:6B1O)
Atropine	−7.18	−6.96	−7.27	−7.11	−6.55
Dinoxin B	−10.39	−4.38	−10.72	−8.55	−5.52
Scopolamine	−8.24	−6.36	−7.75	−6.87	−8.14
Withametelin	−9.31	−8.78	−10.69	−10.06	−7.97
Hyoscyamine	−7.08	−6.43	−7.25	−6.94	−6.62
Withanolides	−8.67	−6.72	−9.29	−9.72	−5.91

2.4. Docking

The docking studies were carried out using AutoDock 4.2.1, installed in a machine running a 2.4 GHz Intel Core 2 Duo processor with 4GB RAM and 160 GB Hard Disk with Linux as the Operating system. The accuracy of the docking technique is evaluated by calculating how closely the lowest energy pose aligns with the docking score (lowest binding energy). To verify the AutoDock docking process, the co-crystallized ligand was removed from each protein's binding site and then re-docked. There was a high degree of concordance between the inhibitor's docking location and the crystal structure. The image analysis and interaction studies were conducted using Discovery Studio.

2.5. Comparing the Docking Scores of the Selected Receptors in contrast to that of the Phytoconstituents

The comparison of the scores obtained after docking studies, revealed the extent to which the receptors and the phytoconstituents interacted amongst themselves. Such an idea in turn suggested the appropriate targets and their befitting ligands to treat breast cancer.

3. Results & Discussion

The docking scores with respect to the phytoconstituents constituting *Cannabis sativa* revealed the strong interaction of THCA with EGFR (PDB ID:1M17) and PARP (PDB ID:5DS3), Naringin with EGFR (PDB ID:1M17) and Estrogen (PDB ID:3ERT), Vitexin with PARP (PDB ID:5DS3) while Strychnine with all the selected receptors.

In case of *Datura metel* L., better interaction was shown by Dinoxin B and Withanolides, each with CDK4/6 (PDB ID:6GS7), Estrogen (PDB ID:3ERT) and PARP (PDB ID:5DS3) while Withametelin with all the selected receptors.

Visual representation of some of the interactions between receptors and phytoconstituents are shown in the Figures 1–6.

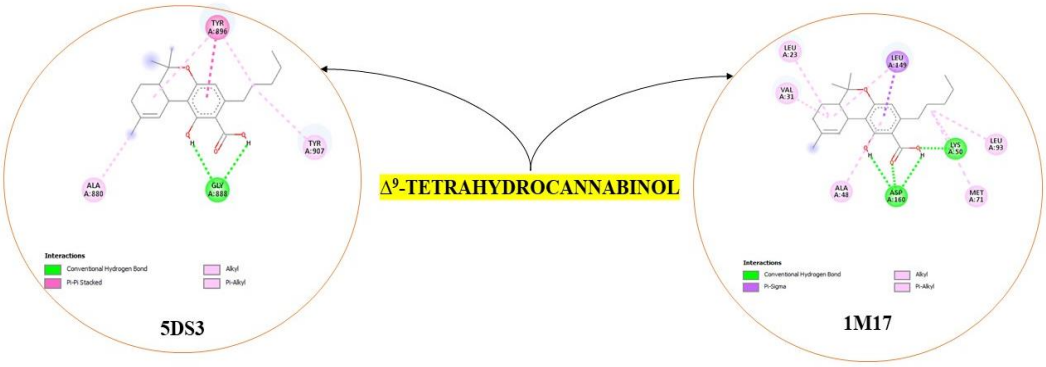

Figure 1. 2D view interaction between Δ⁹-tetrahydrocannabinol and the receptors.

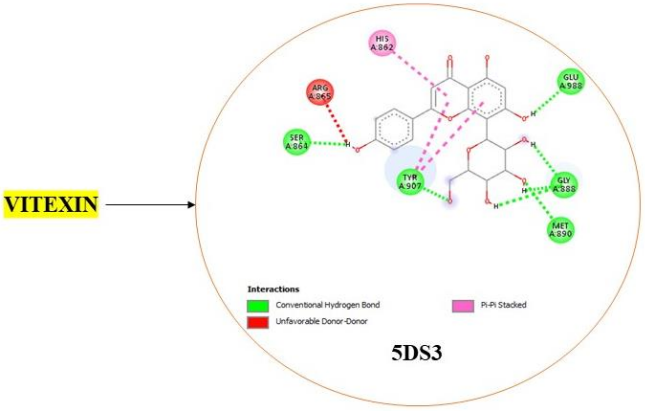

Figure 2. 2D view interaction between Vitexin and 5DS3 receptor.

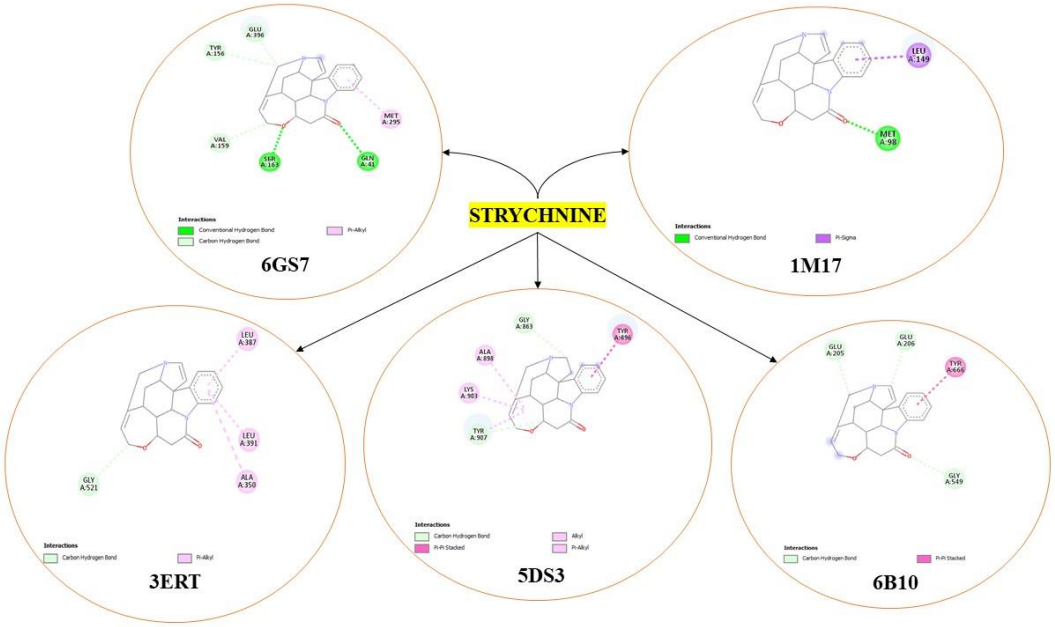

Figure 3. 2D view interaction between Strychnine and the receptors.

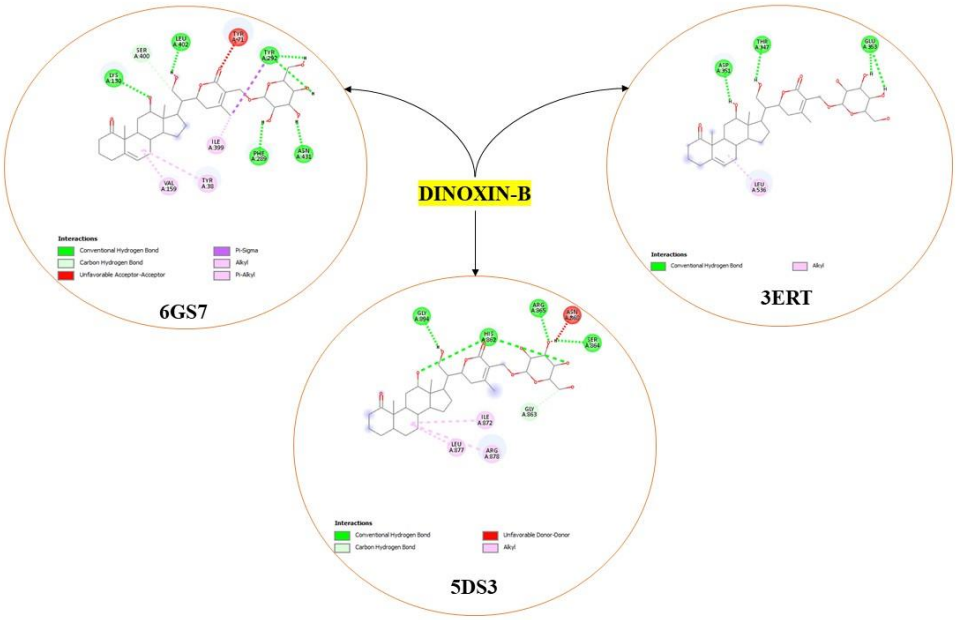

Figure 4. 2D view interaction between Dinoxin-B and the receptors.

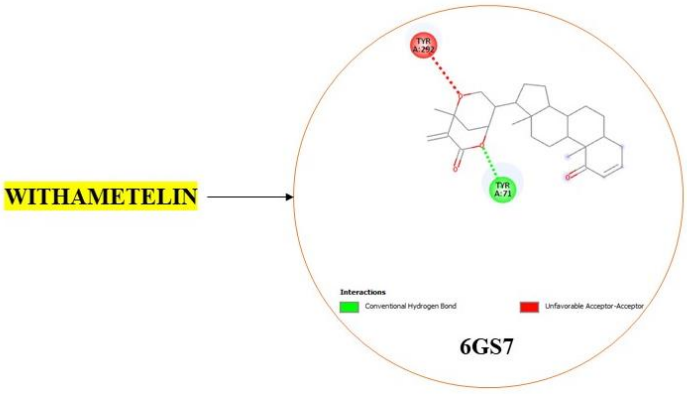

Figure 5. 2D view interaction between Withametelin and 6GS7 receptor.

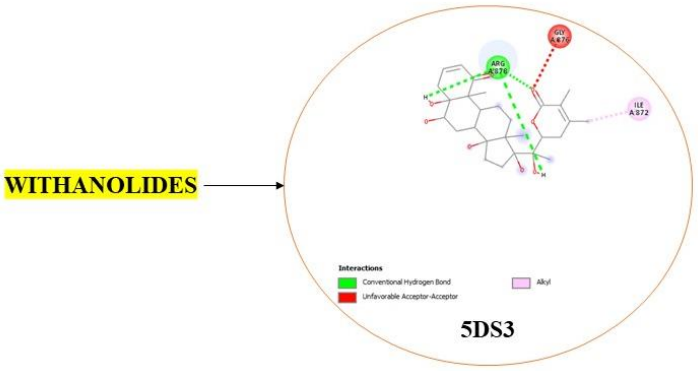

Figure 6. 2D view interaction between Withanolides and 5DS3 receptor.

4. Conclusions

One of the deadliest disease trending till date is cancer. Amidst the various types of the latter, one of the notable ones is breast cancer. Being the most frequently diagnosed and major cause of death in female patients, breast cancer can be treated via chemotherapy, surgery, radiotherapy, etc. However, the synthetic medications used engender unsolicited effects along with the desired ones. To find alternative solutions, we explored few natural resources like the bioactive phytoconstituents of *Cannabis sativa* and *Datura metel* L.

The computational studies highlighted the good interactions between the phytochemicals present in *Cannabis sativa* and the receptors like THCA with EGFR (PDB ID:1M17) and PARP (PDB ID:5DS3), Naringin with EGFR (PDB ID:1M17) and Estrogen (PDB ID:3ERT), Vitexin with PARP (PDB ID:5DS3) while Strychnine with all the selected receptors. Moreover, considering the phytoconstituents within *Datura metel* L., good interaction was also shown by Dinoxin B and Withanolides, each with CDK4/6 (PDB ID:6GS7), Estrogen (PDB ID:3ERT) and PARP (PDB ID:5DS3) while Withametelin with all the selected receptors. Hence, this study underlines the importance of the employment of green chemistry in the drug development arena, with special significance to two such sources having potential to perform as anti-cancer agents.

Author Contributions: Conceptualization, M.G.; methodology, M.G., P.K.; software, M.G.; validation, M.G., P.K.; formal analysis, M.G.; investigation, M.G.; resources, M.G.; data curation, M.G., P.K., S.C.; writing—original draft preparation, S.C.; writing—review and editing, S.C., M.G.; visualization, M.G.; supervision, M.G.; project administration, M.G. All authors have read and agreed to the published version of the manuscript.

Funding: No external funding was received in this research.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflicts of interest.

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