Molecular docking and in-silico predictive analysis of potential herb-drug interactions between *Momordica charantia* and Empagliflozin

Karun Venkatesan Uma¹, Jacob Vineth Martin¹, Gunasekaran Sutheeswaran¹, Raman Rajeshkumar², Sivasankaran Ponnusankar*¹

¹Department of Pharmacy Practice, JSS College of Pharmacy, JSS Academy of Higher Education & Research, Ooty, India.
²Department of Pharmaceutical Biotechnology, JSS College of Pharmacy, JSS Academy of Higher Education & Research, Ooty, India.

**ARTICLE INFO**

Received on: 06/08/2022
Accepted on: 09/01/2023
Available Online: 04/03/2023

**Key words:** Empagliflozin, *Momordica charantia*, herb-drug interactions, molecular docking, simulation, pharmacokinetics.

**ABSTRACT**

The most prominent sequel of multidrug regimens in type 2 diabetes mellitus patients include polypharmacy, non-compliance with medications, and increased financial burden. An extensive study on beneficial herb–drug interactions is required to overcome the above concern. Molecular docking and in-silico approaches can be employed to better understand potential herb–drug interactions. These interactions are presumed to occur at the level of pharmacokinetics. Herbal phytoconstituents can either accelerate or slow down the absorption, distribution, metabolism, excretion and efficacy of a drug. If these interactions are proven to be beneficial, meaning, if they can accelerate the absorption and distribution of the drug and decelerate the metabolism and elimination of the drug, the efficacy of the drug can be increased. As a result, dose escalation, frequency of drug administration, and the addition of anti-diabetic medications to current treatment can be prolonged. This study attempted to computationally analyze the phytoconstituents of *Momordica charantia* for drug likeliness and their binding affinity to specific proteins involved in the pharmacokinetics of Empagliflozin. Additionally, the nature of chemical bonding and binding locations of phytoconstituents and Empagliflozin were studied to understand potential interactions. The findings showed that *M. charantia* and Empagliflozin did not elicit any favorable herb–drug interactions. This is attributed to the non-availability of sophisticated software that can determine the function of the amino-acid binding site. This study necessitates the development of advanced software to determine the function of the amino acid binding site in order to clearly comment on the herb–drug interaction outcome. Also, molecular dynamics and clinical pharmacokinetic investigations with the presented data are encouraged to confirm the findings.

**INTRODUCTION**

According to the International Diabetes Federation Diabetic Atlas 2019, India is positioned among the top 10 countries with 77 million diabetic patients affecting individuals between 20 and 70 years of age (Hyder *et al.*, 2020, 2021a, 2021b). These patients are usually started on a single anti-diabetic agent and eventually, multiple agents are added to the treatment regimen due to the development of insulin resistance. This results in polypharmacy, non-compliance with medications, and a significant increase in the financial burden on the patient. The above concern can be resolved by supplementing diabetic patients with functional foods such as *Momordica charantia* that besides providing nutritive benefits can stimulate the secretion of insulin, and increase the efficacy of anti-diabetic agents by inhibiting the enzymes involved in their metabolism (May and Schindler, 2016). By doing so, such herb–drug interactions can prevent dose escalation, frequency of drug administration, and defer the addition of anti-diabetic agents to the existing therapy. The above inferences can be obtained from the altered pharmacokinetic parameters of the targeted drug. This study attempted to investigate the potential herb–drug interactions between *M. charantia* and Empagliflozin.

It is estimated that about one-third of patients with diabetes mellitus depend on some form of an alternative or

© 2023 Karun Venkatesan Uma *et al*. This is an open access article distributed under the terms of the Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/).
complementary system of medicine for the treatment of type 2 diabetes mellitus (Joseph and Jini, 2013). It is with this impression, that *M. charantia* was chosen as the herb of interest as it is widely used among the Indian population with proven anti-diabetic potential. Empagliflozin was chosen as an exemplary drug counterpart for interaction studies as the literature search signified the few added advantages over other anti-diabetic agents such as the minimal risk of hypoglycemia, better reductions in fasting blood glucose levels, body weight, waist circumference, and diastolic blood pressure (Ferrannini et al., 2013; Marlene Busko, 2014). Further, the study was performed considering the popular hypothesis that herb–drug interactions occur at the level of absorption, distribution, metabolism, excretion (ADME). Hence, the proteins involved in the ADME of Empagliflozin were chosen as the targets for interaction studies. Since no in-silico studies from the literature search demonstrated potential herb–drug interactions between *M. charantia* and Empagliflozin, the in-silico approach was preferred to comment on the altered pharmacokinetics of Empagliflozin.

**MATERIALS AND METHODS**

**Drug likeliness analysis**

The list of phytoconstituents required to perform drug likeliness analysis was collected using Dr. Duke’s Phytochemical and Ethnobotanical Databases (Achutha et al., 2021). The Human Metabolome Database was employed to exclude endogenous substances (Wishart et al., 2016). For a phytoconstituents to exhibit drug likeliness, it should comply with the Lipinski Rule of Five. SwissADME software was used to check compliance with the Lipinski Rule of Five (Daina et al., 2017).

**Selection of targets**

The target proteins were selected based on the fact that phytoconstituent–Empagliflozin interactions occur at the level

| S. No. | Phytoconstituents | Drug likeliness | Absorption | Distribution | Metabolism | Excretion |
|--------|------------------|-----------------|------------|--------------|------------|-----------|
| 1.     | ALPHA-ELEOSTEARIACID | Yes             | GI absorption – high | BBB Permeability – Yes | CYP1A2 inhibitor, CYP2C9 inhibitor | N/A |
| 2.     | ALPHA-SPINASTEROL | Yes             | GI absorption – low | BBB Permeability – No | N/A | -N/A |
| 3.     | BETA-SITOSTEROL | Yes             | GI absorption – low | BBB Permeability – No | N/A | N/A |
| 4.     | BETA-SITOSTEROL-D-GLUCOSIDE | Yes             | GI absorption – low | BBB Permeability – No | N/A | N/A |
| 5.     | DIOSGENIN | Yes             | GI absorption – high | BBB Permeability – Yes | N/A | N/A |
| 6.     | LAURIC-ACID | Yes             | GI absorption – high | BBB Permeability – Yes | N/A | N/A |
| 7.     | STIGMASTEROL | Yes             | GI absorption – low | BBB Permeability – No | CYP2C9 inhibitor | N/A |
| 8.     | CHARINE | Yes             | GI absorption – low | BBB Permeability – No | N/A | N/A |
| 9.     | MOMORDICOSIDE-F-2 | Yes             | GI absorption – low | BBB Permeability – No | N/A | P-gp substrate |
| 10.    | MOMORDICOSIDE-F-1 | Yes             | GI absorption – low | BBB Permeability – No | N/A | P-gp substrate |
| 11.    | MOMORDICOSIDE-G | Yes             | GI absorption – low | BBB Permeability – No | N/A | P-gp substrate |
| 12.    | MOMORDICOSIDE-I | Yes             | GI absorption – low | BBB Permeability – No | N/A | P-gp substrate |
| 13.    | MOMORDICOSIDE-K | Yes             | GI absorption – low | BBB permeability – No | N/A | P-gp substrate |
| 14.    | MOMORDICOSIDE-L | Yes             | GI absorption – Low | BBB permeability – No | N/A | P-gp substrate |
| 15.    | STIGMASTA-7,22-DIEN-3BETA-OL | Yes             | GI absorption – Low | BBB permeability – No | N/A | N/A |
| 16.    | ZEINOXANTHIN | Yes             | GI absorption – Low | BBB permeability – No | N/A | P-gp substrate |

GI: Gastrointestinal; BBB: Blood Brain Barrier; CYP1A2: Cytochrome P450 Family 1 Subfamily A Member 2; CYP2C9: Cytochrome P450 Family 2 Subfamily C Member 9; P-gp: P-glycoprotein; N/A: Not Applicable.
of ADME. The Kyoto Encyclopedia of Genes and Genomes database was used to identify the target proteins (Tao et al., 2020). The selection criteria did not include any absorption proteins as Empagliflozin undergoes passive diffusion. Since Empagliflozin exhibits its pharmacological activity via SGLT2 co-transporter, it was selected. UGT2B7, UGT1A3, UGT1A8, and UGT1A9 were the enzymes involved in the metabolism of Empagliflozin. Similarly, ABCB1 and ABCG2 were the proteins involved in the excretion of Empagliflozin. Hence, these metabolizing and excretory proteins were selected for molecular docking studies.

Molecular docking and molecular visualization

Docking studies were performed using AutoDock Tools v.1.5.6 to identify the binding affinities of phytoconstituents and Empagliflozin toward the proteins of interest. Blind docking was planned and performed to identify the best binding sites. Further, interaction studies were performed using the best configurations obtained from the blind docking of target proteins. According to the study hypothesis, docking scores of phytoconstituents lesser than the docking scores of Empagliflozin were considered for further analysis as they inherently exhibit stable binding and more potential for altering the pharmacokinetics of Empagliflozin. The entire docking results were validated using the molecular visualization software, PyMOL v2.4.1 (Valdés-Tresanco et al., 2020).

Analysis of binding interactions

The stability of an interaction depends on the nature of bonding. The stronger the bond, the greater the stability of the interaction. Hence, the drug and phytoconstituent–protein complexes were analyzed for the nature of bonding. Further, the binding locations of phytoconstituents and Empagliflozin were analyzed. This was considered a crucial step in this study as binding to specific amino-acid residues can either accelerate or terminate the function of a protein. LigPlot+ v.2.2 was used to visualize the binding locations (Mishra and Dey, 2019).

RESULTS AND DISCUSSION

Drug likeliness analysis

A total of 241 phytoconstituents were identified in M. charantia using Dr. Duke’s Phytochemical and Ethnobotanical Databases. These phytoconstituents were present in various parts of the plant like cotyledon, fruit, leaf, pericarp, seed, seed oil, and shoot. Among these, the widely consumed edible portion of the plant is considered to be the fruit of M. charantia. Hence, phytoconstituents in the fruit portion of M. charantia were shortlisted and 97 of them were identified. This list contained a majority of phytoconstituents that were also present in human beings referred to as endogenous substances. A study performed with such endogenous substances can result in bias (difficult to distinguish if the herb–drug interaction has occurred because of the phytoconstituents or the endogenous substances). So, endogenous substances like neurotransmitters (5-hydroxytryptamine, Gamma Amino Butyric Acid), amino acids (alanine, phenylalanine, glutamic acid, proline), polypeptides, vitamins (thiamine, riboflavin, niacin), cholesterol, lanosterol, elements (calcium, copper, iron, magnesium, manganese, nickel, phosphorus, potassium, sodium, titanium, lead), halogens (fluoride, iodine), enzymes (peroxi-

dase), and carbohydrates identified using Human Metabolome Database were excluded. By excluding the above categories, 35 phytoconstituents were obtained. These 35 phytoconstituents were subjected to drug-likeliness analysis. A drug-likeliness analysis with SwissADME software revealed phytoconstituents namely: alpha-eleostearic acid, alpha-spinasterol, beta-sitosterol, beta-sitosteryl-D-glucoside, diosgenin, lauric acid, stigmastanol, charine, momordicoside-F2, momordicoside-F1, momordicoside-G, momordicoside-I, momordicoside-K, momordicoside-L, stigmas-
ta-7,22-dien-3 beta-ol, and zeinoxanthin to comply with Lipinski Rule of Five. To assess if these 16 phytoconstituents had the potential to interact with specific targets of Empagliflozin, their ADME profile was studied (Table 1). This preliminary analysis revealed possible high gastrointestinal (GI) absorption of alpha-eleostearic acid, diosgenin, and lauric acid, the interaction of alpha-eleostearic acid and stigmastanol with CYP1A2 and CYP2C9, and the interaction of momordicoside and zeinoxanthin with permeability glycoprotein (P-gp). The early ADME profile of the phytoconstituents suggested that they had a strong potential to influence the absorption, metabolism, and excretion of Empagliflozin.

Selection of targets

The 3D structures of UGT2B7 (PDB ID: 206L), ABCB1 (PDB ID: 6FN1), and ABCG2 (PDB ID: 6VX1) were retrieved from the Protein Data Bank (PDB). SWISS-MODEL was used to predict the 3D structures for the remaining proteins. This requires the entry of sequence in

Figure 1. 3D structures of proteins predicted using SWISS-MODEL. These predicted structures were further used for molecular docking, visualization studies, and determination of amino-acid binding sites.
| Proteins/ enzymes/target | Phytoconstituents   | Docking scores |
|--------------------------|--------------------|----------------|
| Empagliflozin            | −5.9               |
| Alpha-Spinasterol        | −6.8               |
| Beta-Sitosterol-D-Glucoside | −6.8         |
| Diosgenin                | −7.2               |
| Stigmasterol             | −6.2               |
| Charine                  | −5.9               |
| **UGT2B7**               |                    |
| Momordicoside-F-2        | −7.6               |
| Momordicoside-F-1        | −6.9               |
| Momordicoside-G          | −6.4               |
| Momordicoside-I          | −7.4               |
| Momordicoside-K          | −6.3               |
| Momordicoside-L          | −6.5               |
| Zeinoxanthin             | −5.9               |
| Empagliflozin            | −8.5               |
| **ABCB1**                |                    |
| Diosgenin                | −10.4              |
| Momordicoside-F-1        | −8.8               |
| Empagliflozin            | −7.2               |
| Alpha-Spinasterol        | −7.5               |
| Beta-Sitosterol-D-Glucoside | −7.4         |
| Diosgenin                | −8.8               |
| Stigmasterol             | −7.3               |
| **ABCG2**                |                    |
| Momordicoside-G          | −8.1               |
| Momordicoside-I          | −8.6               |
| Momordicoside-K          | −7.8               |
| Momordicoside-L          | −7.9               |
| Stigmasta-7,22-Dien-3beta-ol | −7.3     |
| Zeinoxanthin             | −8.3               |
| Empagliflozin            | −6.3               |
| Alpha-Spinasterol        | −7.2               |
| Beta-Sitosterol-D-Glucoside | −7.0       |
| Diosgenin                | −9.0               |
| Stigmasterol             | −6.6               |
| **UGT1A3**               |                    |
| Momordicoside-F-2        | −8.1               |
| Momordicoside-F-1        | −7.9               |
| Momordicoside-G          | −7.5               |
| Momordicoside-I          | −8.6               |
| Momordicoside-K          | −7.9               |
| Momordicoside-L          | −6.7               |
| Stigmasta-7,22-Dien-3beta-ol | −6.4      |

*Continued*
FASTA format which was obtained using the UniProt database. The 3D structures of UGT1A3 (P35503), UGT1A8 (Q9HAW9), UGT1A9 (O60656), and SGLT2 (P31639) are depicted in (Fig. 1).

**Molecular docking and molecular visualization**

The study findings demonstrate that a majority of phytoconstituents had a better binding affinity toward UGT2B7 except for charine and zeinoxanthin with maximum affinity expressed by momordicoside-F2 (−7.6). Diosgenin exhibited maximum binding affinity toward ABCB1, ABCG2, UGT1A3, and UGT1A8 with a docking score of −10.4, −8.8, −9.0, and −9.6 respectively. Beta-sitosterol exhibited maximum affinity toward UGT1A9. Momordicoside-F2 exhibited maximum affinity toward SGLT2 with a docking score of −8.9 (Table 2). The PyMOL v2.4.1 results comply with the findings of the docking study (Fig. 2).

**Analysis of binding interactions**

The phytoconstituent-protein complexes and Empagliflozin-protein complexes invariably exhibited hydrogen bonding, a relatively weak bond when compared to an ionic and covalent bond. The binding location results are depicted in Figure 3. From Figure 3a and b, it is evident that Empagliflozin and momordicoside-F-2 share similar non-interacting amino-acid residues indicating that the binding pocket of Empagliflozin is found adjacent to the binding pocket of momordicoside-F-2. Similarly, Figure 3c and d demonstrate that momordicoside-G and momordicoside-I almost share the same non-interacting amino-acid residues indicating that they share almost similar binding pockets. From Figure 3e and f, it is understood that momordicoside-K and momordicoside-L compete for Val450 and Leu454 and completely share similar non-interacting residues indicating that there exists competitive binding between momordicoside-K and momordicoside-L.

**LIMITATIONS**

Although the study was conducted following a sound methodology, it failed to demonstrate potential herb–drug interactions between Empagliflozin and *M. charantia*. This is attributed to the non-availability of software that could assist in identifying the functionality of the amino-acid binding site. Our thorough literature search could find only one software called CASTp v.3.0 that could aid in the identification of the functionality of the amino-acid binding site (Dundas et al., 2006). However, it failed to provide useful information with respect to this study. If this inference was obtained, the exact effect of phytoconstituents on the pharmacokinetics of Empagliflozin would have been predicted. Despite this limitation, the study conferred a catalog of phytoconstituents that had the potential to elicit herb–drug interactions between Empagliflozin and *M. charantia*. Hence, the foremost prospect of the study would be to develop advanced software that helps precisely comment on herb–drug interactions. Further, this study encourages more research into Molecular Dynamics and Clinical Pharmacokinetics of herb–drug interactions with the furnished data. The research findings of

| Proteins/enzymes/target | Phytoconstituents                  | Docking scores |
|-------------------------|-----------------------------------|----------------|
| Empagliflozin           | **UGT1A8**                        | −6.1           |
| Beta-Sitosterol         | **UGT1A8**                        | −7.0           |
| Beta-Sitosterol-D-Glucoside | **UGT1A8**                  | −7.2           |
| Diosgenin               | **UGT1A8**                        | −9.6           |
| Stigmasterol            | **UGT1A8**                        | −7.7           |
| Charine                 | **UGT1A8**                        | −6.1           |
| Momordicoside-F-2       | **UGT1A8**                        | −9.2           |
| Momordicoside-F-1       | **UGT1A8**                        | −7.2           |
| Momordicoside-G         | **UGT1A8**                        | −8.2           |
| Momordicoside-I         | **UGT1A8**                        | −7.1           |
| Momordicoside-K         | **UGT1A8**                        | −7.6           |
| Momordicoside-L         | **UGT1A8**                        | −8.1           |
| Stigmasta-7,22-Dien-3beta-ol | **UGT1A8**                    | −6.8           |
| Empagliflozin           | **UGT1A9**                        | −8.1           |
| Beta-Sitosterol         | **UGT1A9**                        | −9.7           |
| Diosgenin               | **UGT1A9**                        | −9.1           |
| Momordicoside-G         | **UGT1A9**                        | −8.6           |
| Momordicoside-K         | **UGT1A9**                        | −8.1           |
| Empagliflozin           | **UGT1A9**                        | −8.3           |
| Diosgenin               | **UGT1A9**                        | −8.8           |
| Momordicoside-F-2       | **SGLT2**                         | −8.9           |
| Momordicoside-F-1       | **SGLT2**                         | −8.7           |
| Momordicoside-I         | **SGLT2**                         | −8.3           |
| Momordicoside-G         | **SGLT2**                         | −8.6           |
| Momordicoside-K         | **SGLT2**                         | −8.1           |
| Empagliflozin           | **SGLT2**                         | −8.3           |
| Diosgenin               | **SGLT2**                         | −8.8           |

**Table 2**

/Journal of Applied Pharmaceutical Science 13 (03); 2023: 175-182
Figure 2. (a)–(g) Confirm the stable binding of phytoconstituents that exhibited maximum affinity in molecular docking studies.
Figure 3. Different types of binding interactions exhibited by Empagliflozin and phytoconstituents with the proteins of interest. The green circles in (a) and (b), represent that Empagliflozin and momordicoside-F-2 share similar non-interacting amino acid residues. Likewise, green circles in (c), (d), (e), and (f) demonstrate that momordicoside-G and Momordicoside-I; Momordicoside-K and Momordicoside-L share similar binding pockets. The red circles in (e) and (f) indicate that the phytoconstituents momordicoside-K and momordicoside-L compete for the same amino-acid residues Leu454 and Val450 of ABCG2.
such studies can revolutionize the current clinical practice of type 2 diabetes mellitus.

CONCLUSION

The study did not demonstrate any beneficial herb–drug interactions between Empagliflozin and M. charantia. To conclude from the above findings, *Momordica charantia* does not alter the pharmacokinetics of Empagliflozin. However, studies on herb–drug interactions are required to confirm the same in animal models and human volunteers. Molecular dynamics and clinical pharmacokinetic studies with the presented data are appreciated to study the absolute effect of herb–drug interactions in the real-world setting.

ACKNOWLEDGMENT

The authors thank JSS College of Pharmacy, Ooty and JSS Academy of Higher Education & Research, Mysuru for providing all necessary facilities and support to conduct this study.

AUTHOR CONTRIBUTIONS

Uma K V: Conceptualization and design, data acquisition, data analysis and interpretation, drafting the manuscript, and final approval of the manuscript. Vineth Martin J: Data acquisition, data analysis and interpretation, drafting the manuscript, and final approval of the manuscript. Sutheeswaran G: Data acquisition, drafting the manuscript, and final approval of the manuscript. Ponnusankar S: Conceptualization and design, data analysis and interpretation, critical revision of manuscript, supervision, and final approval of the manuscript. Raman Rajeshkumar: Conceptualization and design, data analysis and interpretation, critical revision of manuscript, supervision, and final approval of the manuscript.

LIST OF ABBREVIATIONS

ADME-Absorption, Distribution, Metabolism, Excretion; P-gp, Permeability glycoprotein; PDB, Protein data bank.

FINANCIAL SUPPORT

There is no funding to report.

CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

All data generated and analyzed are included in this research article.

PUBLISHER’S NOTE

This journal remains neutral with regard to jurisdictional claims in published institutional affiliation.

REFERENCES

Achutha A, Pushpa V, Manoj K. Comparative molecular docking studies of phytochemicals as Jak2 inhibitors using Autodock and ArgusLab. Mater Today Proc, 2021; 41:711–6.

Daina A, Michielin O, Zeote V, SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Sci Rep, 2017; 7(1):42717.

Dundas J, Ouyang Z, Tseng J, Binkowski A, Turpaz Y, Liang J. CASTp: computed atlas of surface topography of proteins with structural and topographical mapping of functionally annotated residues. Nucleic Acids Res, 2006; 34(Web Server issue):W116–8.

Ferrannini E, Berk A, Hantel S, Pinnetti S, Hach T, Woerle HJ, Broedl UC. Long-term safety and efficacy of empagliflozin, sitagliptin, and metformin: an active-controlled, parallel-group, randomized, 78-week open-label extension study in patients with type 2 diabetes. Diabetes Care, 2013; 36(12):4015–21.

Hyder KM, Mohan J, Varma V, Ponnusankar S, Raja D. Impact of prediabetes education program on knowledge, attitude and practice among prediabetic population of south India. Prev Med Rep, 2021a; 23:101395.

Hyder KM, Mohan J, Varma V, Sivasankaran P, Raja D. Effects of muscle-specific exercises compared to existing interventions on insulin resistance among prediabetes population of South India. J Nat Sci Biol Med, 2021b; 12(2):230–6.

Joseph B, Jini D. Antidiabetic effects of *Momordica charantia* (bitter melon) and its medicinal potency. Asian Pac J Trop Dis, 2013; 3(2):93–102.

Marlene Busko. Empagliflozin useful second-line for diabetes vs glimepiride [ONLINE]. 2014. Available via: https://www.medscape.com/viewarticle/831846 (Accessed 09 September 2022).

Mishra A, Dey S. Molecular docking studies of a cyclic octapeptide-cyclosaplin from sandalwood. Biomolecules, 2019; 9(11):740.

Tao Q, Du J, Li X, Zeng J, Tan B, Xu J, Lin W, Chen XL. Network pharmacology and molecular docking analysis on molecular targets and mechanisms of Huashi Baidu formula in the treatment of COVID-19. Drug Dev Ind Pharm, 2020; 46(8):1345–53.

Valdés-Tresanco MS, Valdés-Tresanco ME, Valdés-Tresanco MF, Valiente PA, Moreno E. AMDock: a versatile graphical tool for assisting molecular docking with Autodock Vina and Autodock4. Biol Direct, 2020; 15(1):1–12.

Wishart DS, Mandal R, Stanislaus A, Ramirez-Gaona M. Cancer metabolomics and the human metabolome database. Metabolites, 2016; 6(1):10.

How to cite this article:

Uma KV, Martin JV, Sutheeswaran G, Rajeshkumar R, Ponnusankar S. Molecular docking and in-silico predictive analysis of potential herb-drug interactions between *Momordica charantia* and Empagliflozin. J Appl Pharm Sci, 2023; 13(03):175–182.