Kashmir Journal of Science
https:\\kjs.org.pk

Kashmir Journal of Science (2022), 1(1):43-52

Research Paper

Docking Score Function uncovers Arbutin, Berginin and Paullinic Acid as Potential Natural Inhibitors of Human Peroxisome Proliferator-Activated Receptors

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ARTICLE INFO

Article history:

Received: 8 September 2022

Accepted: 14 October 2022

Available online: 02-11-2022

Keywords:

Docking Scoring Function
Peroxisome Proliferator-Activated
Potential Inhibitors
Receptors (hPPARs)

Abstract

Peroxisome proliferator-activated receptor alpha (PPAR-alpha) is a key regulator of lipid homeostasis in hepatocytes and target for fatty acids and hypolipidemic drugs. Different natural molecules from two locally available plants *Trillium govanianum* and *Bergenia ciliatae* were screened virtually using docking scoring function and ADMET properties. The molecular analysis using Molinspiration revealed that these compounds follow Lipinski Rule. These compounds have good absorption, biodegradable, and very low toxicity according to ADMET studies. Docking against the human peroxisome proliferator-activated receptor (hPPARs) obtained from protein data bank (PDB) code 3VI8 which showed that Paullinic acid has the lowest binding energy followed by Berginin and Arbutin. Hopefully, this study will be effective to use these miraculous medicinal plants in drugs to cure infectious and metabolic diseases.

Introduction

Clinical and epidemiological studies in recent years confirmed that degenerative diseases remain a main public health issue and account for more than 38 million (68%) and 56 million deaths in developed as well as in developing countries, respectively. Almost three-quarters of all degenerative diseases and most early deaths (82%) occur in developing countries (Shafiq Ur Rahman, Ismail, Shah, Iriti, & Shahid, 2015; M. X. Wu & Yang, 2017; Ying Liu, 2022; Zou et al., 2013). The most concerning diseases are cancer, cardiovascular, chronic respiratory disease, diabetes, eye, and nerve deterioration, caused due to degradation of the cellular balance between antioxidants and prooxidants (Khan, Siddiq, Akram, & Ashraf, 2018; Yaw, Basir, Talib, Tung, & Nordin, 2013; Yaw et al., 2011). To deal with these degenerative diseases, one of the ways is to improve the antioxidant condition of the body, which can be gained by providing exogenous means of antioxidants (Cole et al., 2006; Zou, et al., 2013). Antioxidants play a significant role in the inhibition and cleansing of radicals, protecting people from infections and degenerative diseases (Muhammad, 2011). On the other hand, in recent years, people are more concerned about the safety of their food and the possible

side effects of synthetic drugs on their physical and mental health. The natural antioxidants from plants are getting the attention of the world due to their safe use. Antioxidants can directly recover or prevent reactive oxygen species (ROS) generation. Recent research has been taking interest in exploring for reported medicinal plant *Trilium govananium* (Shafiq Ur Rahman, et al., 2015) as an antioxidant or to fight against ROS-mediated diseases (Cole, et al., 2006; Heneka et al., 2005; H. Wu et al., 2017; Zhu et al., 2022; Zou, et al., 2013).

Medicinal plant and their parts have been used throughout human history for the treatment of various diseases. The components of medicinal plants are potent to treat infectious, cancerous, gastrointestinal and many other diseases (Shafiq Ur Rahman, et al., 2015). In this study, some components of the root extract of *Trilium govananium* and *Bergenia ciliata* were selected to predict their toxicity potential so that they can be used in the development of various drugs. *T. govananium* belongs to the genus trillium, is widely distributed in the western Himalayas and North America. It has many species worldwide. In Pakistan, it is found at an altitude of 25000-38000m. Many species of this plant are near to extinct because of limited awareness about the importance of this plant (Sinha, Murugesan, Pal, & Saha, 2001). *Bergenia ciliata* is another important medicinal plant found in the temperate region of the Himalayas of Kashmir at a height of 7000-10,000ft. The rhizome of this plant has remarkable impacts against gastro-intestinal problems, kidney stone and malaria (Hafidh et al., 2009). To reveal the importance of components of these study plants, *in-silico* analysis was carried out so that these plants and their parts can be used in the manufacturing of drugs in near future. Absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties of compounds of drugs have a vital role in the development of a drug. Drug discovery is costly and time taking process, most of the drugs failed during clinical trials after their synthesis because of lack of effectiveness and unacceptable toxicity (Cheng et al., 2012). The drug rule of 5, also known as "Lipinski's rule of 5" describes the drug-likeness (Jiang et al., 2012). This rule has become the base for drug discovery. According to this rule, a compound can be used in drug development if it possesses molecular weight less than 500g/mol, a partition coefficient (log p- a measure of hydrophobicity) less than 5, no more than 5 hydrogen bond donors and no more than 10 hydrogen bond acceptors (Al-tel et al., 2011). A compound having less than three of these properties is unlikely to be used as an oral drug (Ahmad, Khan, Akhtar, Khan, & Roy, 2019; Sheikh, Pardeshi, Mujawar, Deshmukh, & Sood, 2015).

The present study was carried out to evaluate the natural inhibiting properties of two commonly found herbs *T. govanianum* and *B. ciliata*, in the Neelum valley of Azad Jammu Kashmir by using docking scoring function. Yet very little research is explored on these two plant roots. As far as our knowledge is concerned, this is the first report by using chemo computing method (Goto et al., 2008). In this study, chemo computing analyses were used for selected components of plant extracts through online available software Molinspiration, Molecule Operating Environment and AdmetSAR.

Methodology

Database Screening for Compound Selection

The chemical compounds Catechin, Gallicin, Arbutin, Camphor, β-Sitosterol were taken from *B. ciliata* and *T. govananium* Diosgenin, Pennogenin, Ecdysone, Paullinic acid and Hexadecatrienoic acid were taken for *in-silico* analysis because these compounds show good antioxidant and anti-microbial activity.

Pubchem Database

The simplified Molecular Input Line Entry System (SMILES) is used to represent the chemical structure of a compound in single line notation. It consists of letters, numbers and characters that specify the atoms, their connectivity and bond order.

Molecular Docking

MOE software has been used for the molecular docking module. Once the ligand-receptor complex is formed, it will adopt the most stable conformation, i.e., the lowest energy level. The purpose of the dock application is to look at favorable conformational binding between medium-size ligands and a not so soft macromolecular target, which is usually a protein (Al-tel, et al., 2011; Goto, et al., 2008). For each compound, several conformations called poses were generated to identify favorable binding modes. The search for binding modes is generally constrained to a small specific region of the receptor called the active site. First docking is without the solvation parameter (without H_2O molecules), the second docking is done considering the presence of H_2O molecules.

ADMET

ADMET properties that are Absorption, Distribution, Metabolism, Excretion and Toxicity of drug candidates play a key role in the development of drugs and environmental hazards assessment. AdmetSAR is an online service that provides information about the carcinogenicity and toxicity of the drug and shows whether a drug follows the Lipinski Rule of 5 or not. To evaluate the toxicity of selected compounds SMILES of relevant ligands were entered in the AdmetSAR program (Nisha et al., 2016).

Results and Discussion

ADMET analysis was performed to evaluate the natural inhibitory properties of the compounds of roots of *B. ciliata* and *T. govananium*. Table 1 and 2 show the AdmetSAR analysis of selected compounds of the above two mentioned plant roots. The toxicity profile of Catechin, Gallicin, Arbutin, β-Sitosterol, Camphor, Linalool, Glucoside, Berginin, Epicatechin-3-O-gallate and Methyl cinnamate from *B. ciliata* and Diosgenin, Pennogenin, Ecdysone, Paullinic acid and Protodioscin from *T. govananium*, were studied by using AdmetSAR software. The results show that none of these compounds is toxic. The ligands Arbutin and β-Sitosterol have log-p value more than 5 which is violation of drug rule of five. In similar way Glucoside and Epicatechin-3-O-gallate have more than five Hydrogen bond doners which is also violation of drug rule of five. However, these compounds could also be used in further studies as one violation in drug rule of five is acceptable. It means Diosgenin and Paullinic acid are having one violation of Drug rule of five that is log p value is greater than five. Ecdysone also have one violation of the drug rule of five by containing more than 5 hydrogen bond doners. Protodioscin have three violation of drug rule of five as Mol. Wt. > 500 Daltons, HBA >10 and HBD > 5, so this compound has very low potential to be a lead compound for a drug (Khan, et al., 2018).

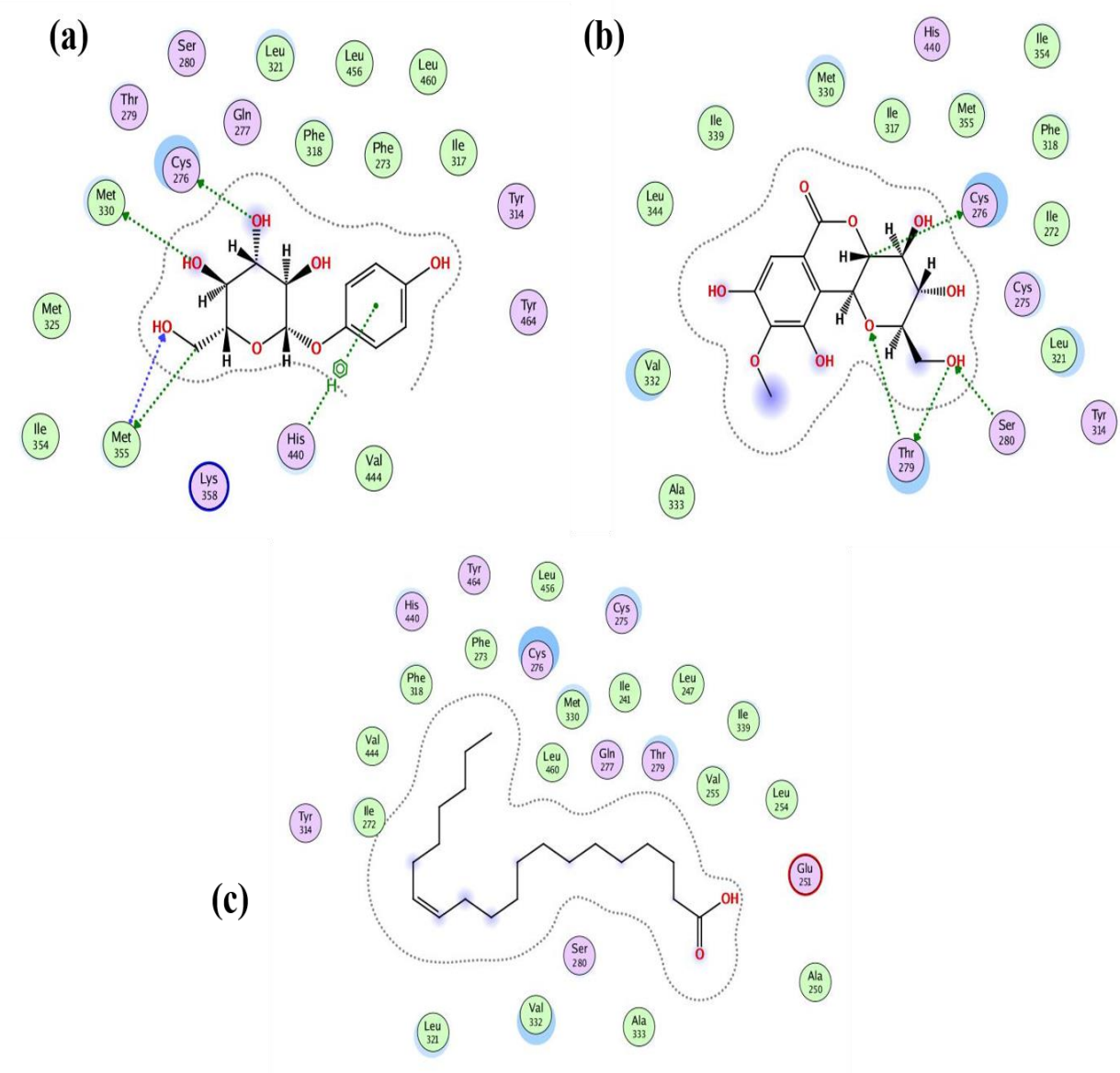

Figure 1: Integration of ligands in pocket of target protein shows good results for these three compounds hence these three compounds could be good potential inhibitors for 3VI8
a) Diagram integration of Protein 3VI8 with Arbutin **b)** Diagram integration of Protein 3VI8 with Berginin **c)** Diagram integration of Protein 3VI8 with Paullinic Acid

Figure 1 illustrates the ligands in pocket of target protein having good results for Arbutin, Berginin and Paullinic Acid, hence these three compounds could be good potential inhibitors for 3VI8. This was done to study whether these two plants can be used to develop drugs in near future. The results indicate that Catechin, Gallicin, Camphor, Linalool, Berginin, Methyl cinnamate and Pennogenin all follow Lipinski's rule, and these can be used for further formulation studies. While Arbutin, β-Sitosterol, Glucoside and Epicatechin-3-O-gallate (compounds obtained from *B. ciliata*). Diosgenin, shows integration of Ecdysone, Paullinic acid and Protodioscin from *T. govananium* do not follow ligands in pocket of target protein. The ligands show good attachment inside the pocket of protein. The AdmetSAR profile of Compounds Catechin, Gallicin, Camphor, Linalool, Berginine, Methyl cinnamate and Pennogenin showed that these compounds follow Lipinski's rule and compounds Arbutin, β-Sitosterol, Epicatechin-3-O-gallate and Glucoside from B.ciliata and Diosgenin, Ecdysone, Paullinic acid and Protodioscin from *T. govananium* failed to follow Lipinski's rule because these compounds have a molecular weight greater than 500 g/mol, Partition coefficient greater than 5,

hydrogen bond acceptor greater than 10. The non-carcinogen nature of these candidates can be helpful to develop anti-cancerous drugs in future. Results of docking are illustrated in Figure 1 and 2 as well as in Table 3 and 4 respectively.

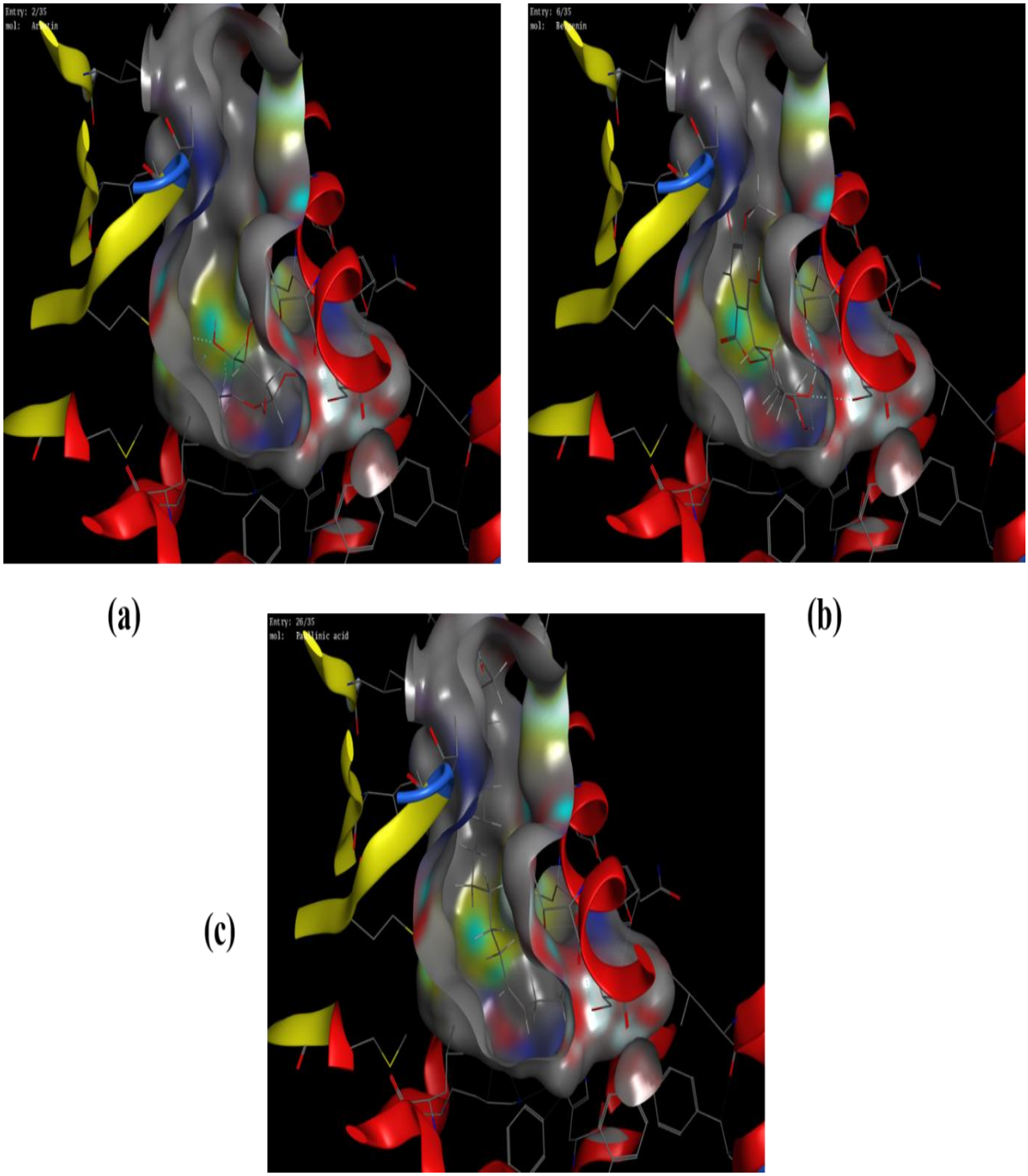

Figure 2: Diagram Integration of ligands in pocket of target protein. The ligands show good attachment inside the pocket of protein

a) Diagram integration of Protein 3VI8 with Arbutin **b)** Diagram integration of Protein 3VI8 with Berginin **c)** Diagram integration of Protein 3VI8 with Paullinic Acid.

Docking Score Function uncovers Arbutin, Berginin and Paullinic Acid

Table 1: The data showing AdmetSAR analysis of ligands of *B. ciliate*.

S.No	Compound	Mol.wt	LogP	HBA	HBD	Topo PSA	Carcinogen	Biodegradable
1.	**Catechin**	290.27	1.37	6	5	110.37	Non Carcinogens	Not ready biodegradable
2.	**Gallicin**	250.33	0.85	3	1	46.5	Non Carcinogens	Ready biodegradable
3.	**Arbutin**	414.72	8.62	1	1	20.23	Non Carcinogens	Ready biodegradable
4.	**Camphor**	152.24	2.16	1	0	17.07	Non Carcinogens	Not ready biodegradable
5.	**β-Sitosterol**	414.72	8.62	1	1	20.23	Non Carcinogens	Not ready biodegradable
6.	**Linalool**	154.25	3.21	1	1	20.23	Non Carcinogens	Ready biodegradable
7.	**Glucoside**	367.31	-1.63	10	**6**	169.54	Non Carcinogens	Not ready biodegradable
8.	**Berginine**	249.8	-0.90	9	5	145.91	Non Carcinogens	Ready biodegradable
9.	**Epicatechin-3-O-gallate**	442.38	2.54	10	**7**	177.13	Non Carcinogens	Not ready biodegradable
10.	**Methyl cinnamate**	162.19	2.53	2	0	26.30	Non Carcinogens	Ready biodegradable

Three compounds from the investigated plants Paullinic acid, Berginin and Arbutin have the lowest binding energies, could be used as a potential drug for hyperlipidemia and inhibitor of hPPARs. This study shows that Paullinic acid, Berginin and Arbutin could be potential drug candidate as an inhibitor of Human peroxisome proliferator-activated receptors in future.

Table 2: The data show AdmetSAR analysis of ligands of *T. govananium*

Sr. No.	Compound	Mol.wt	LogP	HBA	HBD	Topo PSA	Carcinogen	Biodegradable
1.	**Diosgenin**	414.63	**5.93**	3	1	38.70	Non Carcinogens	Not ready biodegradable
2.	**Pennogenin**	430.63	4.99	4	2	58.92	Non Carcinogens	Not ready biodegradable
3.	**Ecdysone**	464.6	1.36	7	**6**	138.44	Non Carcinogens	Not ready biodegradable
4.	**Paullinic acid**	310.52	**8.47**	2	1	37.30	Non Carcinogens	Ready biodegradable
5.	**Protodioscin**	**1049.21**	-0.21	**22**	**13**	346	Non Carcinogens	Ready biodegradable

Table 3: Ligands and their properties used in docking in MOE

	Mol	rseq	Mseq	S	rmsd_ref...	E_conf	E_place
1	**Arbutin**	1	1	-7.1428	2.0843	72.0656	-69.3250
6	**Bergenin**	1	2	-7.1700	1.7221	85.9602	-78.0521
11	**catechin**	1	3	-6.6983	2.0700	-7.3249	-86.8212
16	**diosgenin**	1	4	-4.5734	1.1887	117.4418	-87.8136
21	**Ecdysone**	1	5	-3.9663	1.6292	89.2642	-86.5131
26	**Paullinic ac**	1	6	-9.5089	1.7794	-5.1181	-50.9287
31	**Sitosterol**	1	8	-6.0786	1.8748	161.7292	-77.8030

Table 4: Energy balance of used natural complexes (Kcal/mol) calculated by the docking scoring function. This shows good strong binding energy of the ligands.

	Mol	E_score1	E_refine	E_score2
1	**Arbutin**	-10.8163	-32.4325	-7.1428
6	**Bergenin**	-11.1654	-31.2411	-7.1700
11	**catechin**	-14.3628	-30.9586	-6.6983
16	**diosgenin**	-8.3357	20.1122	-4.5734
21	**Ecdysone**	-6.8592	29.0121	-3.9663
26	**Paullinic ac**	-9.6140	-42.0693	-9.5089
31	**Sitosterol**	-7.9591	6.4941	-6.0786

Conclusion

In conclusion, chemo computing analyses were used for selected components of plant extracts through online available software Molinspiration, Molecule Operating Environment and AdmetSAR. Three compounds from the investigated plants Paullinic acid, Berginin and Arbutin showed the lowest binding energies. So, these could be potential drugs for hyperlipidemia and inhibitor of hPPARs. Five candidates from *B. cilata* and one from *T. govananium* have been screened by the *in-silico* method. These compounds can be used for further studies as probable drug candidates. This software could be

helpful to understand the qualities of the components of the sample before their use in research work or to develop drug from them. Hopefully, findings of this study will be helpful to use these miraculous medicinal plants in drugs to cure infectious and metabolic diseases.

Conflict of interest

The authors declare no conflict of interest.

Contribution

The Manuscript is based on an M.Phil. thesis at the Khan Lab, Department of Chemistry, University of Azad Jammu and Kashmir (UAJ&K), Muzaffarabad, Pakistan. SJ wrote the initial draft of this manuscript. ARK supervised and finalized it. ZA, JK and RAWK helped in data generation, analysis and compiling.

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