Research Journal of Medicinal Plant

ISSN 1819-3455

Academic Journals Inc.

www.academicjournals.com

OPEN ACCESS Research Journal of Medicinal Plants

ISSN 1819-3455
DOI: 10.3923/rjmp.2020.133.143

Research Article
In-silico Evaluation of Wound Healing Potential of *Euphorbia tithymaloides*

[1]Rahul S. Adnaik, [2]Vyankatesh R. Dharanguttikar, [2]Swapnali A. Thorat, [1]Pratibha R. Adnaik, [2]Prajakta D. Nayakal and [2]Sanket S. Patil

[1]Anandi Pharmacy College, Kalambe Tarf Kale, Kolhapur, Maharashtra, India
[2]Rajarambapu College of Pharmacy, Kasegaon, Sangli, Maharashtra, India

Abstract

Background and Objective: The wound healing after the injury is a complex process by which the skin and the tissue under the skin fix themselves. Euphorbia Tithymaloides has various therapeutic uses, such as antiprotozoa, anti-inflammatory, antiplasmodial, antimicrobial and so on. The goal of this study was to predict wound healing medicinal products with a focus on the *in silico* effect of chemical constituents on wound healing process. **Materials and Methods:** *In silico* molecular docking of reducing sugar present in Euphorbia tithymaloides was performed using two receptors of leukotriene such as structural basis of the proinflammatory signaling complex mediated by TSLP PDB ID: 4NN5, Crystal structure of the type-I interleukin-1 receptor complexes with interleukin-1beta PDB ID: 1ITB and second two receptor of NF-κB which are Cryptic glucocorticoid receptor-binding sites pervade genomic NF-κB response elements PDB ID: 5E69 and Structure–function analyses of the bacterial zinc metalloprotease effectors protein GtgA+ uncover key residues required for deactivating NF-B PDB ID:6GGR. **Results:** As a result, D-Ribose has a dock score of-51.51and -75.56 Kcal mol^{-1} against TSLP and interleukin-1 receptor type-I in the first test. And second result D-Ribose dock score of -76.42 and -64.69 Kcal mol^{-1} against two NF-ÿB receptors that predicted interaction with selected protein structure via strong hydrogen bonding, with good docking score ensuring significant binding affinity with selected protein structure. **Conclusion:** The current research offers a significant approach to the reducing sugar derivative's structural requirements that would make it possible for the wound healing mechanism to interact with the receptors concerned.

Key words: *In-silico* molecular docking, inflammatory diseases, phytochemical, inflammatory mediators, signaling complex, pharmacological activities, vasoconstriction

Citation: Rahul S. Adnaik, Vyankatesh R. Dharanguttikar, Swapnali A. Thorat, Pratibha R. Adnaik, Prajakta D. Nayakal and Sanket S. Patil, 2020. *In-silico* evaluation of wound healing potential of *Euphorbia tithymaloides*. Res. J. Med. Plants, 14: 133-143.

Corresponding Author: Rahul S. Adnaik, Anandi Pharmacy College, Kalambe Tarf Kale, Kolhapur, Maharashtra, India

Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Chronic inflammatory disease is a medical situation characterize through chronic inflammation which define as a delayed and determined pro-inflammatory condition is noticeable effectively via new connective tissue formation[1]. Inflammation is explained as the local reaction of living mammalian tissues to injury appropriate mediator. It is body defense reactions categorize into eliminate or limit the spread of injurious agent, follow by elimination of the necrosis cells and tissues[2]. Traditional nonsteroidal anti inflammatory drugs (NSAIDs) represent the most widely prescribed, efficacious and cost-effective pharmacological treatment of rheumatologic and inflammatory disorders. In addition, this class of drugs is widely used to treat mild to moderate pain[3]. Most currently used nonsteroidal anti-inflammatory drugs (NSAIDs) have limitations for therapeutic use since they cause gastrointestinal and renal side effects that are inseparable from their pharmacological activities[4].Wound healing is simply repairing process of injured cells. The dermis and epidermis form a protective barrier against the external environment during undamaged skin. Once the mediator busted the barrier there is development of damages and regulate the sequence of biochemical procedures be situate to cure/repair the damage. External wound healing is a complex procedure with four important stages that occur constantly. The first stage i.e. Hemostasis is occurs right away after the injury to stop the bleeding by platelet aggregation and platelet-mediated vasoconstriction[5].

In the second stage (Inflammation), the injured tissue cells and capillaries activate the release and function of several cytokines which induce phagocytosis to remove debris and initiate wound repair. Inflammation is local response of living tissues to injury due to foreign matter. It is a body defense reaction to prevent the spread of injurious agent. Inflammation is the growth of fluid, leukocytes and inflammatory mediators such as cytokines[6]. In the third stage (Proliferative stage), the wound surface is enclosed with a new epithelium (Epithelization) and granulation tissues with new vascularization are formed to repair the injured tissue. In last stage (Maturation) the collagen is remolded and wound fully closes. The cells which used in wound healing are no longer. They are removed by apoptosis. *Euphorbia tithymaloides* is commonly known as Lady's Slipper Flower and scientifically known as *Pedilanthus tithymaloid. Euphorbia tithymaloides* is a medicinal plant applied to wounds for rapid healing. Euphorbia Tithymaloid (ET) is a perennial succulent spurge. It is native to tropical and sub-tropical North America and Central America[7]. These shrubs a re 6-8 feet long and 18-24 inch wide. ET grows in fertilized sandy soil rich in metal concentration like boron, copper, iron, manganese, molybdenum and zinc. Their leaves are alternate, sessile, glabrous and acuminate in shape[8]. It is a carcinogenic plant thus has the ability to grow in toxic soil very easily and rapidly. Sometimes, ET is also used to remediate soil and can be used as border of garden. In this study Ribose from the leaves of ET were characterized in terms of their structural properties[9].

Ribose is the sugar of the pentose class which occurs naturally as a chemical constituent in *Euphorbia tithymaloides* which have ability of wound healing after binding to the specific receptor. Ribose-taurine (Rib-T) put off the growth of inflammatory mediators. (Rib-T) shows anti-inflammatory action by inhibiting nuclear translocation of nuclear factor-kappa B (NF-κB) p65and NF-κB DNA-binding effect in the anti-inflammatory activity. Rib-T shows anti-inflammatory activity associated with NF-κB regulation[10]. Receptors are the any part of a cell, usually a large protein molecule, on the cell surface or in the cytoplasm with which a drug molecule interacts to trigger a response or effect. Leukotriene and NFKB are the receptors with which riboses (drug molecule) interact and shows wound healing activity[11]. By predicting the analysis of these constituents of Euphorbia tithymaloides acts as the most effective anti-inflammatory agents for wound healing and it also verified that the reduced sugar portion evaluated in silico molecular docking has a powerful anti-inflammatory potential by conducting this research.

MATERIALS AND METHODS

Molecular docking study

Hardware and Software used: All the computational studies were executed by the PC windows 7 ultimate with Intel Core i5 microprocessor, 4 GB memory and 32 Bit operating system. Biological databases were used such as PubChem, PDB (Protein Data Bank) and Vlife QSAR BioPredict tool software used for molecular dockings and this software study were performed in Rajarambapu College of Pharmacy, Kasegaon in month of Jun, 2019. Thus the structure of Sucrose, D-Maltose, D-Mannose, D-Galactose, D-Glucose, D-Ribose, D-Xylose, Sorbitol, D-Fructose and D-Arabinose was confirmed by spectrometric techniques[12]. Further t hey are evaluated for *in silico* molecular docking to investigate its anti-inflammatory potential i.e., wound healing activity.

***In silico* molecular docking of *Euphorbia tithymaloide* constituent against leukotriene and NFKB proteins files selection:** Molecular docking studies were performed by using Vlife MDS 4.6.1 version. Where the protein were used for this

study are of two different types which are responsible to wound healing and the receptors searched such as structural basis of the pro-inflammatory signaling complex mediated by TSLP PDB ID: 4NN5 second is Crystal structure of the type-I interleukin-1 receptor complexed with interleukin-1beta PDB ID: 1ITB and NFKB two receptor which are found as Cryptic glucocorticoid receptor-binding sites pervade genomic NF-κB response elements PDB ID: 5E69 and Structure–function analyses of the bacterial zinc metalloprotease effectors protein GtgA uncover key residues required for deactivating NF-B PDB ID: 6GGR were obtained from the Protein Data Bank (www.rcsb.com). The receptor extracted by X-ray diffraction method with having resolution less than 2.5A°. These structures contain four complexes were determined with molecular replacement method using AMoRe. The coordinates of native C-lobe (Protein Data Bank code: 1NKX) were used as the search model. The rotation and translation search functions were calculated with data between the resolution ranges in between of 12.0-4.0 A°[13].

Ligand preparation: Ligand of Sucrose, D-Maltose, D-Mannose, D-Galactose, D-Glucose, D-Ribose, D-Xylose, Sorbitol, D-Fructose and D-Arabinose isolated from *Euphorbia tithymaloide* plant constituents were drawn[14]. 2D structure of ligand was prepared and converted to 3D by Chem Draw Ultra 8.0 software. Then farther these 3D structures were constructed to energy minimization process by using batch optimization for a set of molecules. MMFF is used for molecular mechanics. For that process the parameter set as 10,000 as Maximum number of cycles, 0.01 as Convergence Criteria, 1.0 as Constant (medium's dielectric constant which is 1 for in vacuo). Select MMFF from Force Field drop down list. For MMFF Force Field, the MMFF atomic charges get automatically selected. Set the value 20 and 10 respectively for electrostatic and vdW interaction. Conformers of the compounds were generated by systematic search method. The docking results were ranked according to the decreasing docking energies of the different possible conformers for each of the ligends[15].

Docking methodology

Parameters for scoring functions: For the molecular docking study the Parameters set as mode of dock process running is exhaustive and input Rotation Angle step size of 30° by which the ligand will be rotated for different poses. Input Number of Placements as 30 and Ligand wise Results as 5 to obtain 5 top poses for each ligand. The docking scoring function, Escore, is defined by the following energy terms:

$$Escore = Einter+Eintra$$

where, Einter is the ligand-protein interaction energy, Eintra is the internal energy of the ligand[15].

Re-ranking score function: Re-ranking score used was computationally more expensive than the scoring function used during the docking simulation but it is generally better than the docking score function at determining the best pose among several poses originating from the same ligand. Whereas the re-rank score in Vlife calculate approximately strength of the interaction, it was not calibrated in chemical units and it didn't get complex contributions (such as entropy) into report. The free energy of binding (FEB) was defined as the sum of final intermolecular energies (Van Der Waals+Hydrogen bond+Desolvation energy), final total internal energy, torsional free energy and unbound system's energy[16].

Interpretation of results: Lastly, the analysis starts by measuring the minimum dock score of ligand and interaction between the atoms present in ligand (i.e., atoms present in different plant phytochemical constituents) and amino acid isolated by docking technique from receptors. In this system correlation of bond interaction present on atoms and receptors, four forms of interaction were mainly observed such as Van Dar Waals interaction, charged interaction, pi-stacking interaction and hydrogen bonding (as in the study the maximum number of hydrogen bonding observed was considered as the ligand and protein interaction is stronger) so this binding score and interaction will succeed Predict wound healing activity of the respective plants[17].

RESULTS

The molecular activity values, based on the predictive ability of the molecules with different receptors coupled with the wound healing cycle. The ligand 2D and 3D structure of Sucrose, D-Maltose, D-Mannose, D-Galactose, D-Glucose, D-Ribose, D-Xylose, Sorbitol, D-Fructose and D-Arabinose was completed by spectrometric validation methods shown in Fig. 1 and 2. Thus the drug-receptor binding interpretation is determined on the basis of the docking results which are shown in (Table 1 and 2). Table 1 summarizes the findings of the docking study of 10 bioactive components of *Euphorbia tithymaloide* with the receptor as structural basis of the pro-inflammatory signaling complex regulated by TSLP PDB ID: 4NN5 and second is Type-I interleukin-1 receptor complex

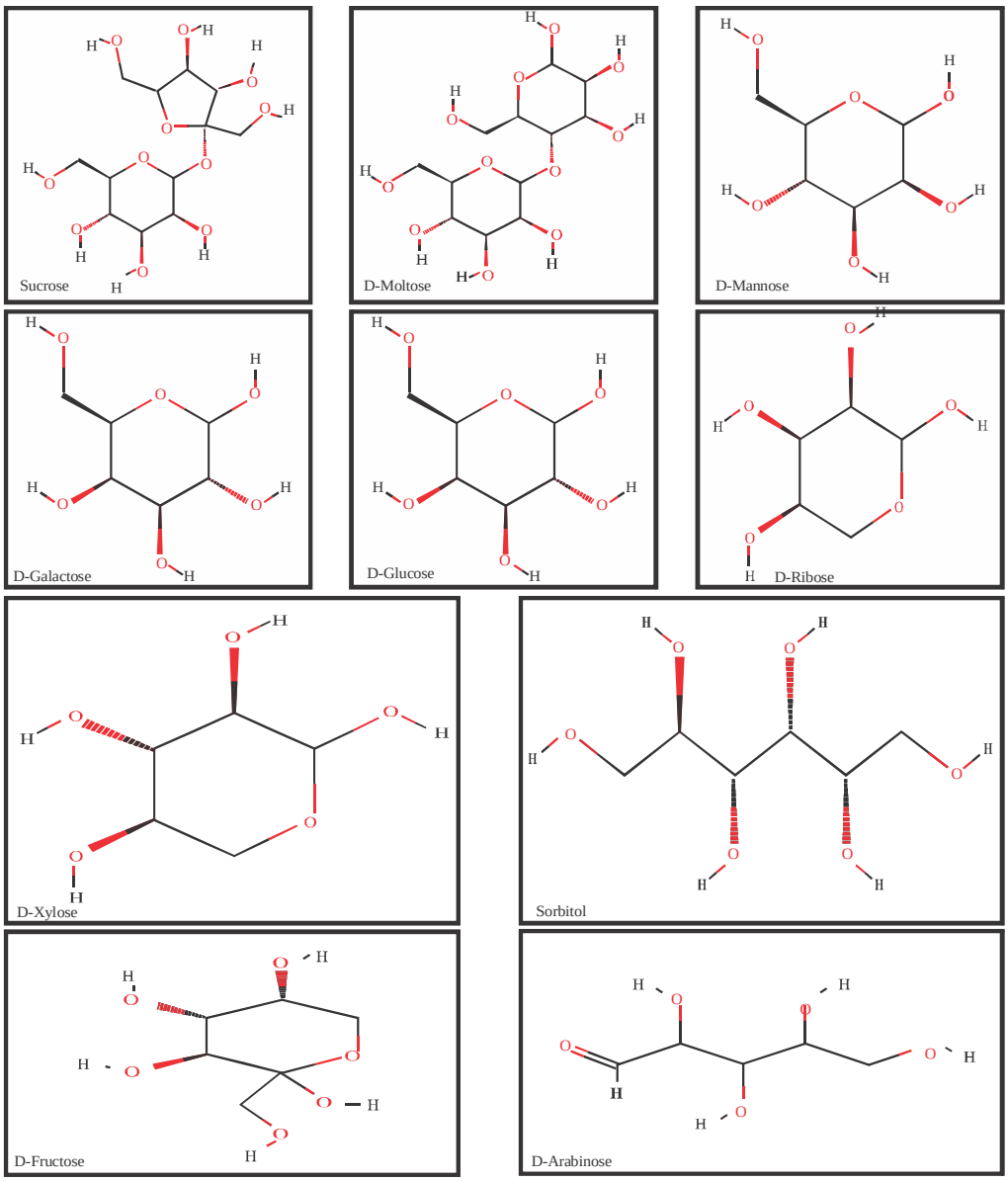

Fig. 1: Structures of bioactive compound present in *Euphorbia tithymaloide*

Table 1: Molecular docking results of bioactive constituents present in *Euphorbia tithymaloide* with leukotriene receptors

			Dock score	
Molecule	Final energy	Final GRMS value	4NN5	1ITB
Sucrose	117.0440	0.8750	-27.89	-51.85
D-Maltose	90.4100	0.6642	-43.23	-56.38
D-Mannose	47.7400	0.8775	-26.44	-38.01
D-Galactose	45.0880	0.7957	-25.61	-39.57
D-Glucose	44.7461	0.9157	-28.52	-38.95
D-Ribose	-37.9008	0.9161	-51.51	-75.56
D-Xylose	31.5016	0.7505	-19.24	-32.32
Sorbitol	45.1167	0.8750	-26.89	-40.88
D-Fructose	37.8695	0.5960	-29.67	-43.13
D-Arabinose	30.0214	0.8955	-26.62	-38.62

GRMS*: Conjugate gradient optimization until a root mean squared deviation of the gradient (GRMS) of 0.01 kcal mol^{-1}.Å

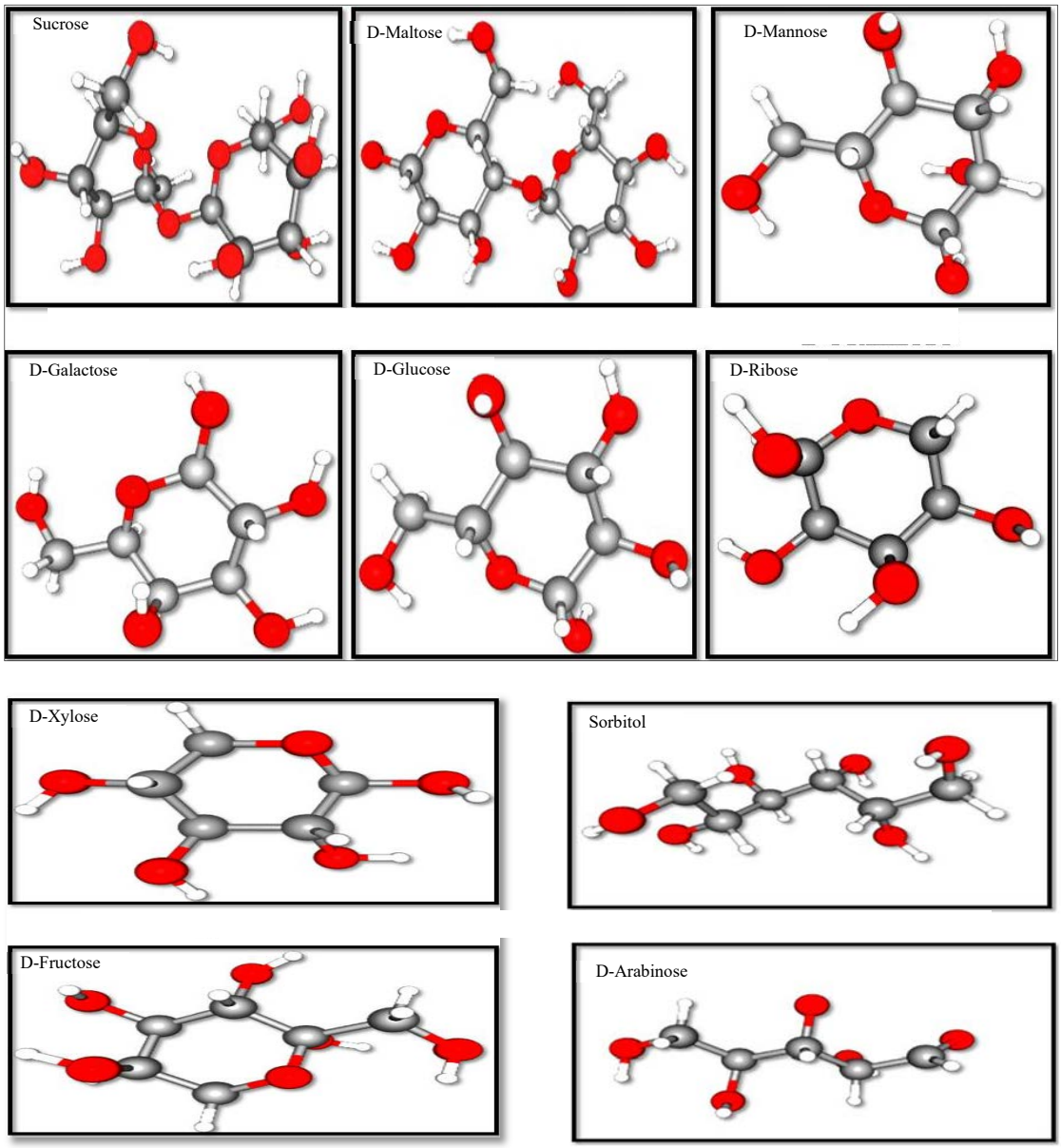

Fig. 2: 3D Structure of ligands molecules present in *Euphorbia tithymaloide*

Table 2: Molecular docking results of bioactive constituents present in *Euphorbia tithymaloide* with NF-κB receptors

			Dock score	
Molecule	Final energy	Final GRMS value	4NN5	1ITB
Sucrose	117.0440	0.8750	-49.97	-49.35
D-Maltose	90.4100	0.6642	-51.68	-55.48
D-Mannose	47.7400	0.8775	-29.64	-26.07
D-Galactose	45.0880	0.7957	-31.36	-25.86
D-Glucose	44.7461	0.9157	-31.43	-28.02
D-Ribose	-37.9008	0.9161	-76.42	-64.69
D-Xylose	31.5016	0.7505	-25.42	-20.47
Sorbitol	45.1167	0.8750	-30.39	-30.39
D-Fructose	37.8695	0.5960	-33.27	-32.74
D-Arabinose	30.0214	0.8955	-30.14	-24.24

GRMS*: Conjugate gradient optimization until a root mean squared deviation of the gradient (GRMS) of 0.01 kcal mol^{-1}.Å

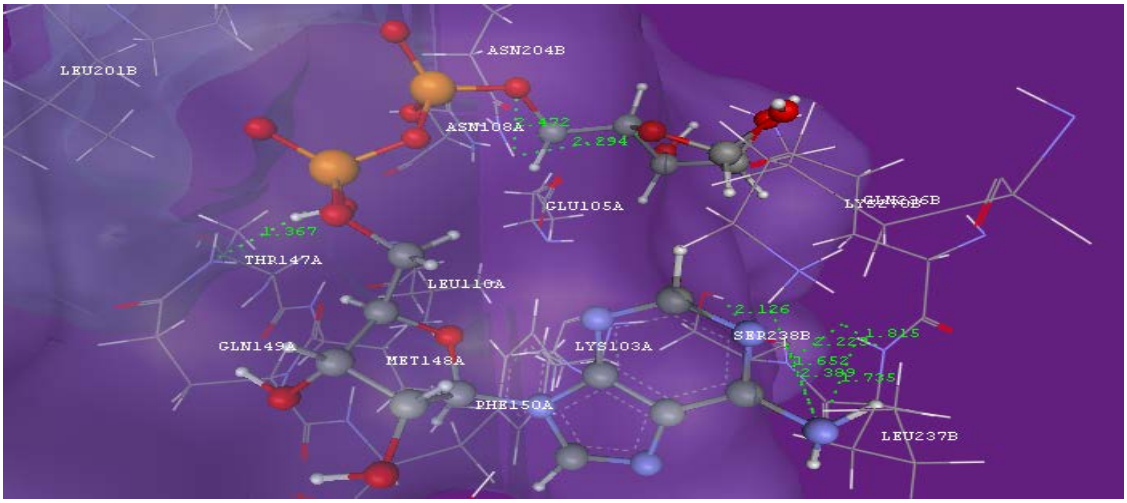

Fig. 3: 3D Dock poses of D-Ribose with leukotriene receptor having PDB ID: 1ITB

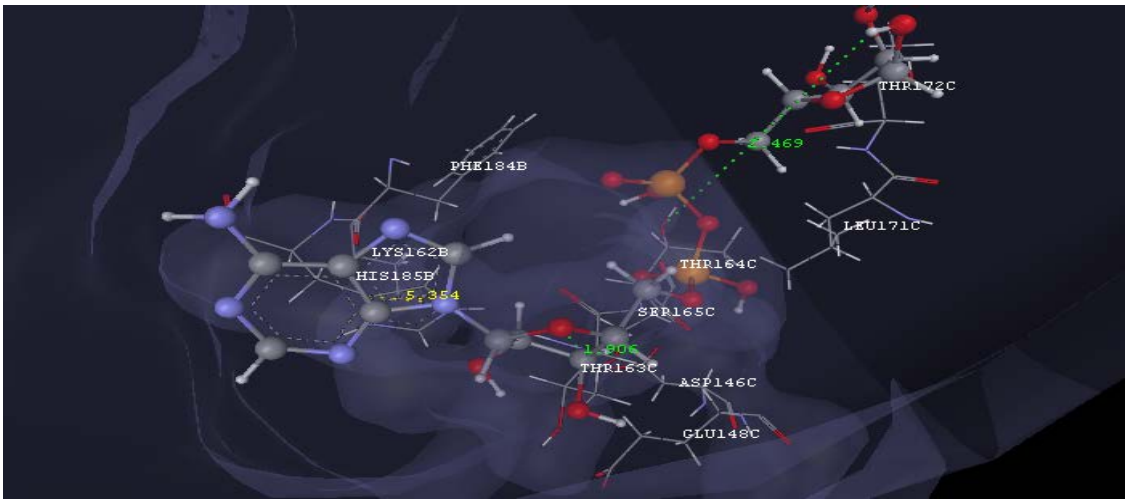

Fig. 4: 3D Dock poses of D-Ribose with leukotriene receptor having PDB ID: 4NN5

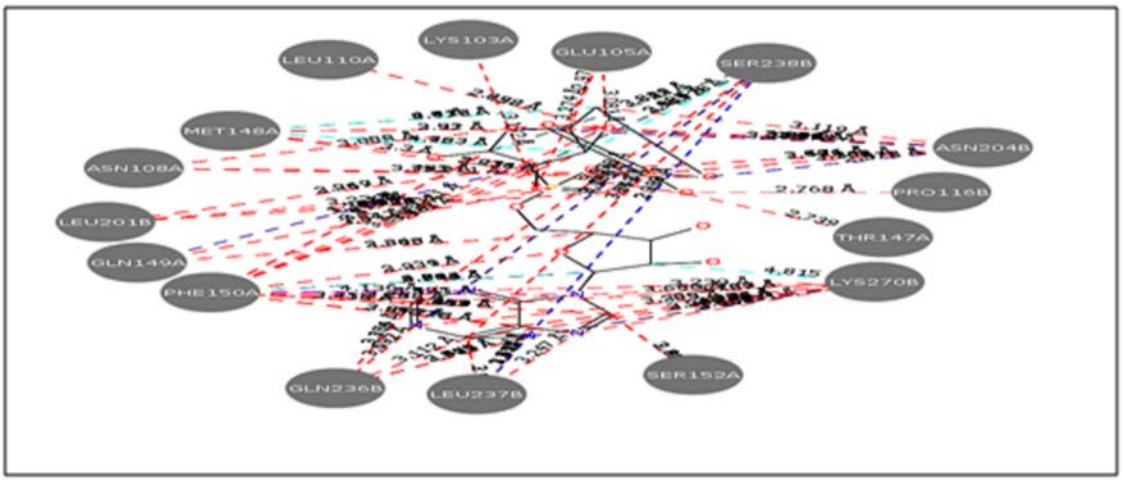

Fig. 5: 2D Interactions pose of D-Ribose with leukotriene receptor having PDB ID: 1ITB

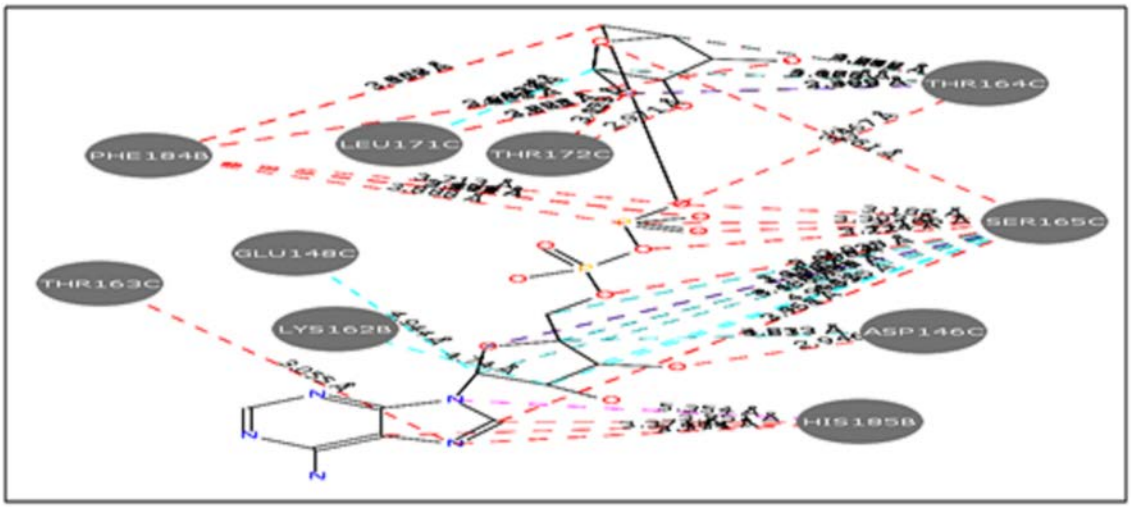

Fig. 6: 2D Interactions pose of D-Ribose with leukotriene receptor having PDB ID: 4NN5

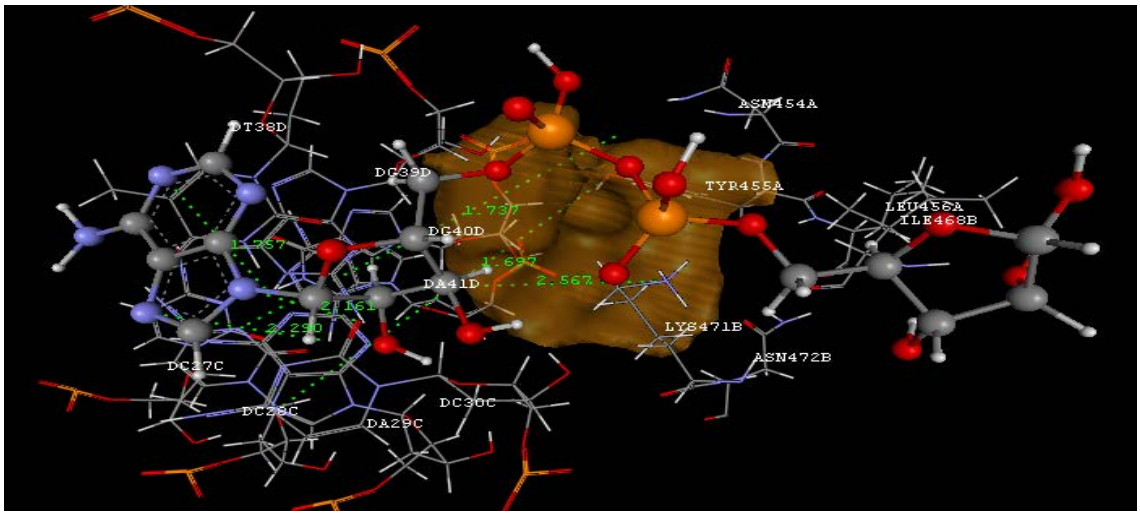

Fig. 7: 3D Dock poses of D-Ribose with NF-κB receptor having PDB ID: 5E69

crystal structure with interleukin-1beta PDB ID: 1ITB. 10 Bioactive components of the *Euphorbia tithymaloide* have receptor affinity 1ITB and 4NN5 none of these have reported Pi stacking interactions. The docked ligands scores of D-Ribose shows the best- docking score -51.51and -75.56 kcal mol^{-1} with their respective receptors such as 4NN5 and 1ITB, accordingly. The D-Ribose has nine H-bonding interactions with the 1ITB receptor with forming amino acid bond such as GLN149A, ASN204B, ASN204B, LEU237B, LEU237B, SER238B, SER238Band LYS270B, They shows two H-bonding interactions with 4NN5 by bonding the amino acid such as THR164C, SER165C. D-Ribose's best-scoring pose did not exhibit hydrophobic interactions. The 3D visualization of D-Ribose's best-docked pose with 1ITB and 4NN5 is also illustrated in Fig. 3 and 4, respectively, by the amino acid interaction shown in Fig. 5 and 6.

Table 2 shows the second docking analysis of 10 bioactive components of *Euphorbia tithymaloide* with the receptor such as Cryptic glucocorticoid receptor binding sites pervade PDB ID: 5E69 and Structure–function analysis of the bacterial zinc metalloprotease effectors protein GtgA reveal key residues needed to deactivate NF-B PDB ID: 6GGR. *Euphorbia tithymaloid's* bioactive components have an attraction for receptor 5E69 and 6GGR no receptor displays Pi stacking and hydrophobic interactions. The docked ligands scores range from -20 to -76 Kcal mol^{-1}, with the best-scored ligand again is D-Ribose with a docking score of -76.42 and -64.69 Kcal mol^{-1} with their respective receptors including

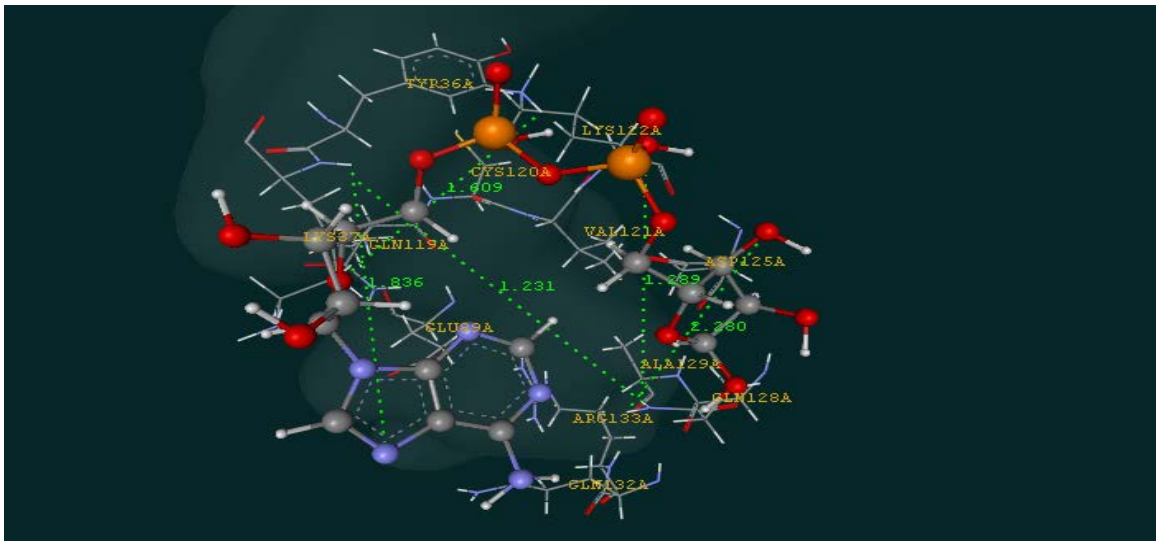

Fig. 8: 3D Dock poses of D-Ribose with NF-κB receptor having PDB ID: 6GGR

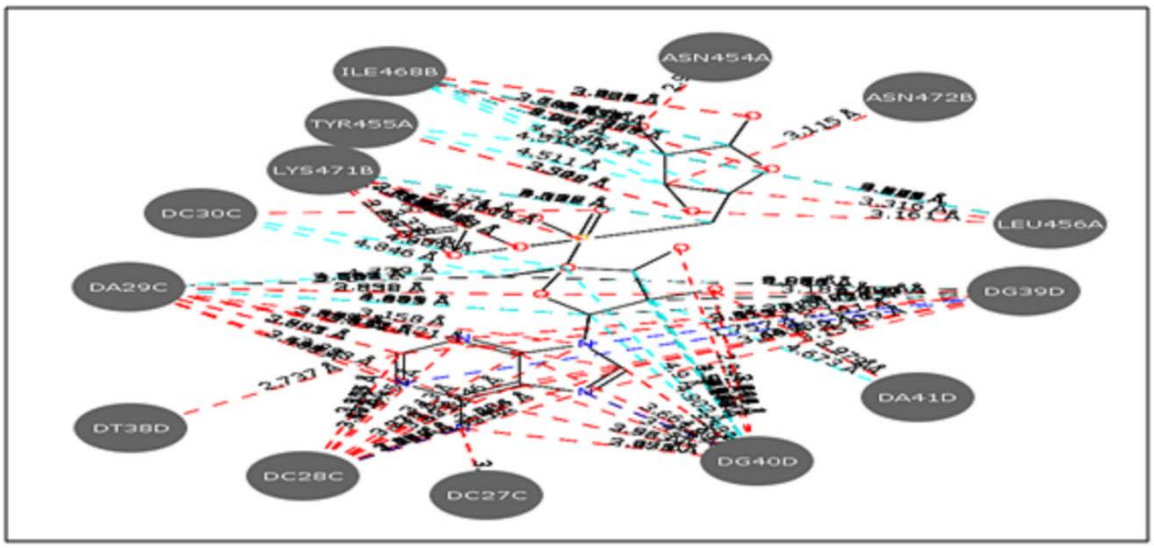

Fig. 9: 2D Interactions pose of D-Ribose with NF-κB receptor having PDB ID: 5E69

5E69 and 6GGR. The D- Ribose has six H-interactions with the 5E69 receptor with amino acid forming bond such as DC28C, DC28C, DG39D, DG39D, DG40D and LYS471B with forming five H-interactions with 6GGR by bonding the amino acid such as LYS37A, LYS122A, GLN128A, GLN128A and GLN128A. D-Ribose's best-scoring position has demonstrated no hydrophobic interactions. The 3D visualization of D-Ribose's best-docked pose with PDB ID: 5E69 and PDB ID: 6GGR is also illustrated in Fig.7 and 8, respectively, by the amino acid interaction shown in Fig. 9 and 10.

DISCUSSION

All 10 reducing sugar derivatives have been tested for their ability to promote wound healing by analyzing their binding interactions with the various proteins that play specific roles in the different stages of wound healing in the human body; unlike the docked ligand, the compounds were docked into each of the various proteins and their binding interactions were evaluated. For this reason, the 10 bioactive constituents identified in the *Euphorbia tithymaloide* plant were compared with those of the native ligand for the purpose behind

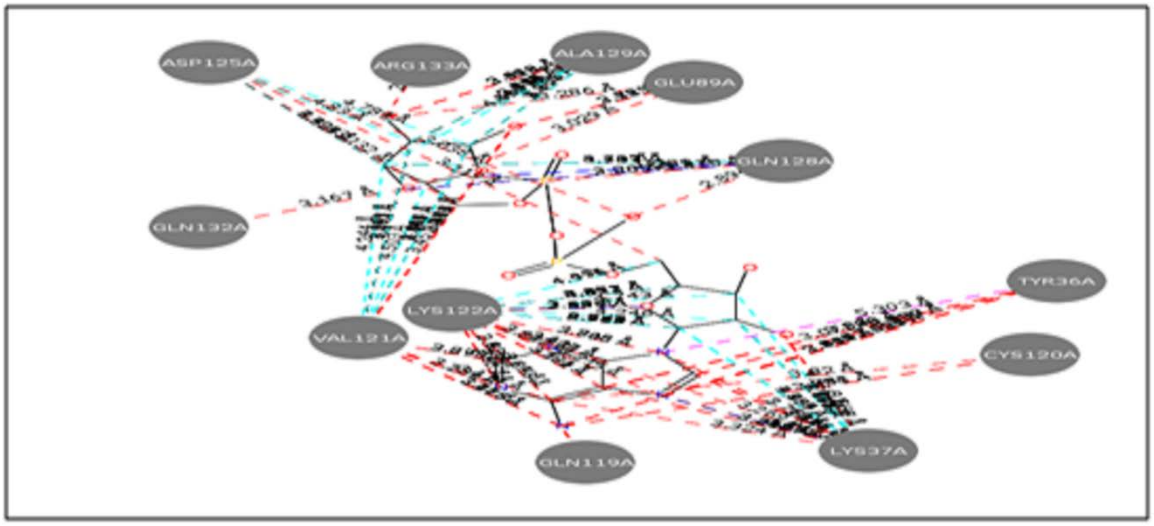

Fig.10: 2D Interactions pose of D-Ribose with NF-κB receptor having PDB ID: 6GGR

validation and interactions. The behaviors of the molecules studied were predicted based on their ability to dock into the receptor's active site. Theoretically all the ligand molecules showed encouraging binding energy and docking score. Among them, the docking against receptor 1ITB and 4NN5 with interacted amino acid with minimum docking score and is considered a strong affinity to bind with interleukin-1 receptor complex inhibitor. The outcomes of the docking analysis of bioactive constituents with the receptor such as Type-I interleukin-1 receptor and TSLP having PDB ID: 1ITB and PDB ID: 4NN5 respectively. The ligand was deeply docked by strong interaction in binding pocket area the dock score ranging from -19 to -75 kcal mol^{-1}. The active compound D-Ribose binds to the receptor at a mol dock score of-51.51and -75.56 kcal mol^{-1} with their respective receptors named as PDB.ID: 1ITB and 4NN5 (Table 1). It binds to the PDB.ID:1ITB receptor showing nine H-bond interactions GLN149A, ASN204B, ASN204B, LEU237B, SER238B, SER238Band LYS270B is the amino acid in cavity 2 (Fig. 3, Fig. 5) and has only two hydrogen bond interactions with the receptor PDB.ID: 4NN5 the amino acid is THR164C and SER165C (Fig. 4, Fig. 6). Analysis of the receptor/ligand complex models developed after successful D-Ribose docking was based on parameters such as hydrogen bond interactions compared to the previously mentioned literature[13]. Similarly D-maltose had a mole. Dock score of -43.23 and -56.38 Kcal mol^{-1} and the van-dar wall bond interactions were low as compared to that of D-Ribose. Compounds like D-Mannose and D-Arabinose display very less Mol. Dock score and thus have a significantly lower affinity to the target. For D-maltose the van-dar wall bond value was -56.38 Kcal mol^{-1}. There are 9 amino acid residues involved in association with D-maltose from various domains of the inhibitor complex interleukin-1 receptor. A compound D-Ribose shows binding energy -51.51and -75.56 Kcal mol^{-1} in these docking studies and it is high as compared to entagenic acid showed minimum binding (-8.79 kJ mol^{-1}) and docking (-8.95 kJ mol^{-1}) in the previous research[7]. Both work findings are therefore expressed for action on wound healing. Thus both research work results are expressed for wound healing activity. Table 2 tabulated second docking analysis of the ligands. The different interaction energies, such as van der Waals energy, intermolecular hydrogen bonding were calculated for each minimized complex. Dock scores for 10 ligands of reducing sugar *Euphorbia tithymaloide* plant range from -20 to -76 Kcal mol^{-1} to Mysterious glucocorticoid receptor PDB ID: 5E69 and bacterial zinc metalloprotease effectors GtgA PDB ID: 6GGR protein[17]. The D-Ribose dock scores docked against Mysterious glucocorticoid shown as -76.42 Kcal mol^{-1} and dock score against the GtgA protein effectors of receptor bacterial zinc metalloprotease are found to be as -64.69 Kcal mol^{-1}[15]. These compounds from the plant *Euphorbia tithymaloide* indicated that the compounds had the highest binding potential when docking against the respective protein structure. Residues DC28C, DC28C, DG39D, DG39D, DG40Dand LYS471B present in the protein, PDB ID: 6GGR play an important role in receptor binding interaction with ligands in which all are H-bond interactions were revealed from the conformational analysis of several docked complexes[4]. Five H-Bond interactions with 6GGR are also observed by bonding the amino acids LYS37A, LYS122A,

GLN128A, GLN128Aand GLN128A[1]. 3D view of best-docked D-Ribose site with PDB ID: 5E69 and PDB ID: 6GGR Fig. 7 and 8 the 2D view is shown in Fig. 9 and 10. D- Ribose is stated to have a wide variety of biological applications for wound healing agents and anti-inflammatory activity. Developing D-Ribose as a possible inhibitor will aid in successful wound treatment with limited or lower toxic effects. Thus the present research has been an attempt to computationally classify compounds that can bind to the essential anti-inflammatory activity targets. The research state that docking scores and their analysis of compound interactions indicate that most of the compounds are capable of binding to multiple targets involved in inflammatory hyperalgesia and regulation of it. With this prediction we go to the experimental evaluation of compounds such as D-Ribose, D-Mannose and D-Arabinose, etc., by practical approaches will lead us to clinically successful molecules for treating various chronic pain disorders.

CONCLUSION

In the present *in silico* research work, the pharmacology involved in between the wound healing process and it was observed that the reported bioactive such reducing sugar constituent's isolated form *Euphorbia tithymaloide* showed effectual interactions with the amino acid residues present in the active binding site of the proteins, leukotriene and NF-κB. This was shown for the conductively inhibitory effects of these constituents towards the respective receptors. The results thus provide an insight for the structure of the ribose which is in *Euphorbia tithymaloide* constituent's that would assist their activity as wound healing agents. Subsequently, the in house extracted phytochemical constituents can be properly formulated into a pharmaceutical dosage form that can be efficiently used for the treatment of different types of wounds.

SIGNIFICANCE STATEMENT

This study discover the significant approach to the structural requirements of the reducing sugar derivative that would make possible their interaction with the receptors concerned to the wound healing process.

REFERENCES

1. de Pedro, M., S. Baeza, M . T. Escudero, T. Dierssen-Sotos, I. Gómez-Acebo, M. Pollán and J. Llorca, 2015. Effect of COX-2 inhibitors and other non-steroidal inflammatory drugs on breast cancer risk: a meta-analysis. Breast Cancer Res. Treat., 149: 525-536.
2. Hafeez A., U. Jain, P. Sajwan, S. Srivastava and A. Thakur, 2013. Evaluation of Carrageenan induced anti-inflammatory activity of ethanolic extract of bark of Ficus virens Linn. in swiss albino mice. J. Phyto.pharma, 2: 39-43.
3. Eming, S.A., T. Krieg and J.M. Davidson, 2007. Inflammation in wound repair: Molecular and cellular mechanisms. J. Invest. Dermatol., 127: 514-525.
4. Dharshan K., 2018. Docking studies for assessment of whealing potential of Dalethyne Derivatives: an in silico approach. Compu. Bio. Bioinfo., 6: 36-50.
5. Periayah, M.H., A.S. Halim and A.Z.M. Saad, 2017. Mechanism action of platelets and crucial blood coagulation pathways in hemostasis. Int. J. Hematol.-Oncol. Stem Cell Res., 11: 319-327.
6. Khatri C.K., K.S. Indalkar, C .R. Patil, S.N. Goyal and G.U. Chaturbhuj, 2017. Novel 2-phenyl-4,5,6,7-tetrahydro[b]benzothiophene analogues as selective COX-2 inhibitors: design, synthesis, anti-inflammatory evaluation and molecular docking studies. Bio. org. Med. Chem .Lett., 27: 1721-1726.
7. Vidya, S.M., V. Krishna, B.K. Manjunatha, B.R. Bharath, K.P. Rajesh, H. Manjunatha and K.L. Mankani, 2012. Wound healing phytoconstituents from seed kernel of *Entada pursaetha* DC. and their molecular docking studies with glycogen synthase kinase 3-β. Med. Chem. Res., 21: 3195-3203.
8. Jawade A., S. Pingle, R. Tumane, A. Sharma, A. Ramteke, R. Jain, 2016. Isolation and characterization of lectin from the leaves of Euphorbia tithymaloides (L.). Tro. Plant. Res. 3: 634-641.
9. Ghosh, S., A. Samanta, N.B. Mandal, S. Bannerjee and D. Chattopadhyay, 2012. Evaluation of the wound healing activity of methanol extract of *Pedilanthus tithymaloides* (L.) Poit leaf and its isolated active constituents in topical formulation. J. Ethnopharmacol., 142: 714-722.
10. Hudson W.H., I.M.S. De Vera, J.C. Nwachukwu, E.R. Weikum and A.G. Herbst *et al*., 2018. Cryptic glucocorticoid receptor-binding sites pervade genomic NF-κB response elements. Nat. Commun., 10.1038/s41467-018-03780-1.
11. Jennings E., D. Esposito, K. Rittinger and T.L.M. Thurston, 2018. Structure–function analyses of the bacterial zinc metalloprotease effector protein GtgA uncover key residues required for deactivating NF-κB. J. Biol. Chem., 293: 15316-15329.
12. Srivastava R. and N. Soni, 2019. An updated review on phytopharmacological profile of Euphorbia tithymaloides (L.) Poit. The Pharma Innovation J., 8: 109-115.
13. Chopade A.R., 2015. Molecular docking studies of phytocompounds from phyllanthus species as potential cpain modulators. Sci. Pharm., 83: 243-267.

14. C. Sundaravadivelan, M.N. Padmanabhan, P. Sivaprasath and L.Kishmu, 2012. Biosynthesized silver nanoparticles from Pedilanthus tithymaloides leaf extract with anti-developmental activity against larval instars of Aedes aegypti L. (Diptera; Culicidae). Parasitol Res., 112: 303-311.
15. Du X., Y. Li, Y.L. Xia, S.M. Ai, J. Liang, P. Sang, X.L. Ji and S.Q. Liu, 2016. Insights into protein–ligand interactions: mechanisms, modelsand methods. Int. J. Mol. Sci., 10.3390/ijms17020144.
16. Verstraete K., L.V. Schie, L. Vyncke, Y. Bloch, J. Tavernier, E. Pauwels, F. Peelman and S.N. Savvides, 2014. Structural basis of the proinflammatory signaling complex mediated by TSLP. Nat. Struct. Mol. Biol., 21: 375-382.
17. Vigers G., L. Anderson, P. Caffes and B. Brandhuber, 1997. Crystal structure of the type-I interleukin-1 receptor complexed with interleukin-1β. nature, 386: 190-194.