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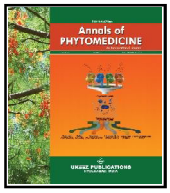

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Network pharmacology based mapping of potential pharmacological mechanism of metabolic profiles of *Tagetes erecta* L. against oxidative and inflammatory stress including associated complication

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Abstract

Tagetes erecta L. is a traditional Indian medicinal plant that has been grown for its various commercial and decorative purpose including immense medicinal properties. Traditionally, it is used as an antioxidant, antidiabetic, neuroprotective, diuretic, *etc*. Due to the lack of scientific evidence based on molecular mechanism of *T. erecta* involved in the alleviation of oxidative stress-induced inflammation and associated complication, thus generating the multitargeted therapeutic evidence using various approaches. Network pharmacology and gene ontology analysis were performed to explore its multimechanistic and therapeutic action in oxidative and inflammatory stress-induced several pathophysiological morbidities. *In silico* docking analyses were performed for further validation of screened phytoconstituents to investigate the biological interaction with NOX antioxidant enzyme. Swiss ADME analysis was performed to investigate the pharmacokinetic behaviour of screened metabolites. Our results of network pharmacology showed the multi-mechanistic and therapeutic role of Tagetes metabolites against pathophysiological pathways such as oxidative stress, inflammation, chronic kidney disease, brain disorder, leukopenia, *etc*., and thus providing Tagetes as a potential herbal drug for alleviating several acute and chronic disease. Swiss ADME analysis revealed significant distribution and skin permeability with log Kp value of eucalyptol (-5.3), limonene (-3.89), linalool (-5.13), methyl eugenol (-5.6) and alpha pinene (-3.95). Hence, it can be concluded that Tagetes contains several metabolites that potentially exhibited positive biological regulation against several morbidities *via* reducing oxidative and inflammatory stress.

1. Introduction

Traditional herbal remedies have contributed immensely to the treatment of a variety of disorders for ages as they possess a diversity of phytoconstituents and numerous medicinal properties. Moreover, medicinal herbs with various phytochemicals have a widespread expansion in their uses since ancient times. They are relatively inexpensive and are less harmful to human health as compared to allopathic medicines (Bushra *et al*., 2020; Gautam *et al*., 2021). Herbal medicines are regarded as valuable sources of drug precursor molecules, which can be used to develop novel treatments. Some indigenous healthcare systems, on the other hand, use herbal medications in unusual ways. Some indigenous healthcare systems, on the other hand, use herbal medications in unusual ways. Safety, quality, effectiveness and efficacy evaluation and empirical scientific evidences collection are all essential components of their legal frameworks (Rasheed and Gupta, 2010; Mallick *et al*., 2015). *T. erecta* is one of the traditional Indian medicinal plant has been used as antioxidant, antidiabetic, neuroprotective, diuretic, *etc*., it possess several verities of the phytochemicals belongs to the category of carotenoids, terpenoids, polyphenols and glycosides, *etc*., which strongly emphasised to make *T. erecta* as one of the medicinally active plant (Yasheshwar *et al*., 2017). *T. erecta* is grown for therapeutic, nutritive, and commercial applications in addition to their decorative significance. Marigold petals are high in natural phytochemicals like carotenoids, lutein, as well as a variety of secondary bioactive molecules. *T. erecta* has been reported to possess compounds such as flavonoid, saponins, triterpene, alcohol, carotenoid, tannins and sterol, mucilage, and resin. These secondary metabolites have been studied for potential agents to exhibit antioxidant activities both enzymatic and non-enzymatic Various secondary metabolites of from *Tagetes* are believed to be effective for one's health and wellbeing (Siriamornpun *et al*., 2012). Through, enzymatic and non-enzymatic processes, these secondary metabolites can quench reactive oxygen species. One such unified approach to the antioxidant mechanism becomes critical in safeguarding biomolecules, which are critical for the overall growth and development of the plant. Secondary bioactive compounds such as ascorbic acid, carotenoid, phenolic compounds, and tocopherols have all been demonstrated to play a direct role in improving health (Berger, 2005; Galieni *et al*., 2015). Free radical quenching based activities (Manju and Pushpa, 2020; Vedam *et al*. (2019) have been consistently assessed for herbal medicinal properties (Ali, 2020; Alam, 2019) not only for human health but also in animal husbandry (Barman *et al*., 2021).

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It is difficult to ascertain the precise mechanism of phytoconstituents that have been demonstrated within treatment intervention for the management of specific or non-specific body ailments from a therapeutic approach. Certain phytochemicals from the selected plant extract are subjected to phytochemical screening, and analytical or quantitative assays, which provide the kind of verifiable facts about the therapeutic intervention generated either by particular phytonutrients inside the plant extract (Nugroho *et al*., 2017; Bhattacharya *et al*., 2002; Yang *et al*., 2015).

Molecular docking is extensively used in the bioinformatics-based study to anticipate non-covalent interactions (mostly hydrogen bonding) of macromolecules (receptors) with ligands for high-throughput screening and structure-based drug discovery (drug molecule) (OLEG TROTT and Schroer, 2010). The drug design process relies on *in silico* computational approaches to assess the overall binding compatibility of a freshly produced compound or one extracted from environmental assets with the specific proteins or genes implicated in ailments (Chandra *et al*., 2018; Islam *et al*., 2013). Autodock is a docking and virtual screening tool that generates the grid for the required atom categories internally. Autodock Vina is a newer version that improves Autodock4 by an order of magnitude in terms of binding pose prediction accuracy and speed (OLEG TROTT and Schroer, 2010). This is the most widely utilized method for identifying potent bioactive phytoconstituents using substantial quantities of experimental plant data, including metabolomics data, and creating molecular-based pharmacological information for prospective use (Yi *et al*., 2018; Zhang *et al*., 2019).

For effective action and metabolism, and efficient drug can be consumed at the desired time and deployed throughout the body. Another issue is toxicity, which is often highly important and influences medication absorption, distribution, metabolism, and excretion. According to research, drugs fail in clinical trials due to undesirable side effects and toxicity, which has been demonstrated to be very costly and time-consuming in medication development. ADME/TOX and drug-likeness prediction *in silico* aid in the identification of new targets and compounds with expected biological activity (Cheng *et al*., 2019). The topological polar surface area (TPSA) denotes the surfaces of the compound's polar atoms and molecules. The lowest permeability of the membrane is associated with a higher TPSA score. Reduced TPSA was helpful for a drug-like property because compounds with a higher TPSA value are a stronger substrate for p-glycoprotein, which is responsible for drug efflux from the cell (Blake, 2000). The blood-brain barrier [BBB] is utilized to determine the vasculature of the CNS. The endothelial cell in the CNS vessel does not have pores, and it has numerous qualities that limit the flow of ions, molecules, and cells, making the CNS vessel very obstructive and interfering with the delivery of chemicals in the central nervous system (Daneman and Prat, 2015).

T. erecta is one of the traditional Indian medicinal plant has been used as antioxidant, antidiabetic, neuroprotective, diuretic, *etc.* It possess several verities of the phytochemicals belongs to the category of carotenoids, terpenoids, polyphenols and glycosides, *etc*., which strongly emphasised to make *T. erecta* as one of the medicinally active plant (Yasheshwar *et al*., 2017).

The present work aims to explore molecular docking study of *T. erecta* bioactive compounds involved in antioxidant radical scavenging activities and thereby assess drug discovery and designing through an *in silico* approach. This was accompanied by molecular interaction analysis (hydrogen bond prediction between target and drugs), drug-likeness behaviour, and ADME/TOX modelling to confirm the efficiency and efficacy of these active compounds. The present study support the *T. erecta* to lay a sustainable basis for future studies on investigating its phytopharmacology frameworks based on the findings and their relevance to the molecular-based potential antioxidant activity of phytochemical compounds.

2. Materials and Methods

2.1 Software information

SwissADME tool, Cytoscape (Version 3.8.2), Autodock Vina (Version 1.5.7), Network Analyst (https://www.networkanalyst.ca). Metascape

2.2 Selection of active constituents from *T. erecta*

A total of 23 metabolites identified form GC-MS analysis in *T. erecta* in our earlier published research article were selected for the study. The screened compounds were limonene, methyl eugenol, linalool, 1,8-cineole or eucalyptol, alpha-pinene, *etc*. (Yasheshwar *et al*., 2017).

2.3 Network pharmacology analysis

Potential interacted target genes were screened through the integration analysis of the compound-gene network. The screened compound targets were imported into the STRING database (https://string-db.org/), a software used mainly for functional enrichment and interaction network analysis of genes. Further, the integration analysis was performed using Cytoscape version 3.8.2. Protein-protein interactions (PPI) network and compound-proteins interactions (CPI) were constructed and interaction information based on the number of nodes, the number of edges, average node degree, and average local clustering coefficient were determined for constructed PPI. The analysis covered all the nearly functional interactions among the expressed proteins-proteins and compound-proteins network (Gaurav *et al*., 2022).

2.4 *In silico* autodock analysis for determination of the antioxidant activity of *T. erecta*

2.4.1 Accession of the target protein

The three-dimensional structure of the targeted protein was found in RCSB Protein Data Bank (http://www.rcsb.org/pdb; ID-6rmj and 1n26, respectively).

2.4.2 Ligand preparation of *T. erecta*

The ligands 3-D SDF file format were retrieved from Pub Chem (https://pubchem.ncbi.nlm.nih.gov/compound/47965) and converted to PDB and PDBQT formats utilizing software (BIOVIA Discovery Studio Visualizer 2021). They were then analysed for molecular docking utilizing Autodock by adjusting torsion, ionization, degree of freedom, and stereo-chemical variation (Rahman *et al*., 2019).

2.4.3 Selection of proteins for docking

The Autodock has been used to construct and optimize the structure of proteins that were identified (Rajalakshmanan *et al*., 2021). The structure of the protein was downloaded in PDB format with a resolution of 1.7 A0 with R-values of 0.222 and 0.171, respectively, for free and work. Autodock Vina and BIOVIA Discovery Studio Visualizer tools were used to accomplishing molecular docking. Before the docking analysis, the command Prompt and precondition were used to process the docking analysis (Islam *et al*., 2013).

2.4.4 Swiss ADME analysis

"Swiss ADME (http://www.swissadme.ch/index.php)" and ProTox-II- chemicals toxicity prediction tool (https://tox-new.charite.de/protox II/index.php?site=home) were used to determine ADME (absorption, distribution, metabolism, and excretion) and toxicological evaluation for phytochemical compounds of the *Tagetes erecta*. In the ADME response of phytochemicals, TPSA (Topological Polar Surface Area (TPSA) for drug property, lipophilicity as for drug Consensus Log Po/w, skin permeability as Log Kp, and drug-likeness were predicted (Daina and Zoete, 2016).

3. Results

3.1 Network pharmacology analysis

3.1.1 Common target network (protein-protein interaction)

The multifunctional role of various compounds was investigated using network pharmacological experiments. The STRING database (https://string-db.org/) and Cytoscape (version 3.8.2) software were used to create PPI and CPI networks, which were interpreted based on ligation efficacy or interaction between protein-protein and protein-compound interactions. The study looked at all of the nearly functional interactions between the expressed proteins and compound proteins (Li *et al*., 2021; Yi *et al*., 2018). The results of this analysis revealed that the chosen genes had a strong connection with one another. There were 41 potential target genes identified by the network. The gene-gene interaction network is designed with a median confidence level of 0.400 in PPI analysis. The network had 14 nodes, 31 edges, an average node degree of 4.43, an average local clustering coefficient of 0.743, and an anticipated number of edges of 2, and a PPI enrichment p-value of 1.0e-16. The edges in the diagram represent the interaction between groups of possible targets, whereas the nodes represent the genes that are being targeted. Figure 1reveals the PPI network as under:

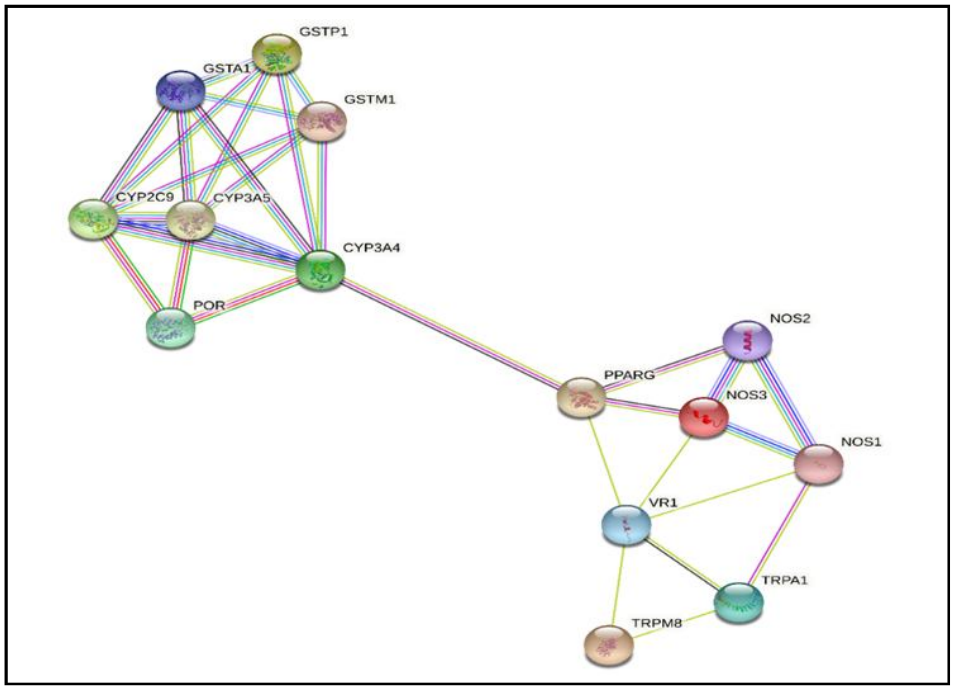

Figure 1: Protein-protein interaction network shows enriched gene interaction with black edges.

3.1.2 Active metabolites target genes network

The bioactive metabolites and target gene-linked network was built, and the study's findings demonstrated that each *T. erecta*metabolite can interact with each gene. The significant GO terms with p.05 were shown, and the protein type was set to Homo sapiens. Edges that were directly associated with the active metabolites became identifiable in our analysis, but the edges that vanished were associated with each target (Figure 2). Methyl eugenol was discovered to have a high interaction with GSTA1, GSTP1, and GSTM1 targets. They were reported to play an important part in stimulus-response, metabolism, and positive regulation of biological mechanisms, detoxification, and other processes. CYP3A5, CYP3A4, VR1, TRPA1, and TRPM8 were discovered to interact with 1, 8 cineole/ Eucalyptol. NOS1, NOS2, NOS3, POR, CYP2C9, and PPARG have all been reported to interact with limonene. Linalool interacts with the proteins TP53, NOS1, NOS2, NOS3, TRPA1, HMGCR, TRPM8, and POR. Alpha pinene was discovered to interact with the enzymes CYP2B6, LHRPL5, and GOLGB1. Figure 2 depicts the developed network of bioactive compounds and their targets genes and genes with protein id are given in Table 1.

Table 1: List of selected genes with UniProt id

Sr. No.	Gene name	Protein name	UniProt id
1.	NOS2	Nitric oxide synthase, inducible	P35228
2.	CYP3A5	Cytochrome P450 3A5	P20815
3.	GSTP1	Glutathione S-transferase P	P09211
4.	PP53	-	-
5.	GSTM1	Glutathione S-transferase Mu 1	P09488
6.	PPARG	Peroxisome proliferator-activated receptor gamma	P37231
7.	CYP2C9	Cytochrome P450 2C9	P11712
8.	NOS3	Nitric oxide synthase, endothelial	P29474
9.	CYP3A4	P08684	P08684
10.	TRPM8	Transient receptor potential cation channel subfamily M member 8	Q7Z2W7
11.	HMGCP	--	-
12.	TRPA1	Transient receptor potential cation channel subfamily A member 1	TRPA1
13.	POR	NADPH—cytochrome P450 reductase	P16435
14.	VR1	-	-
15.	NOS1	Nitric oxide synthase, brain	P29475
16.	GSTA1	Glutathione S-transferase A1	P08263

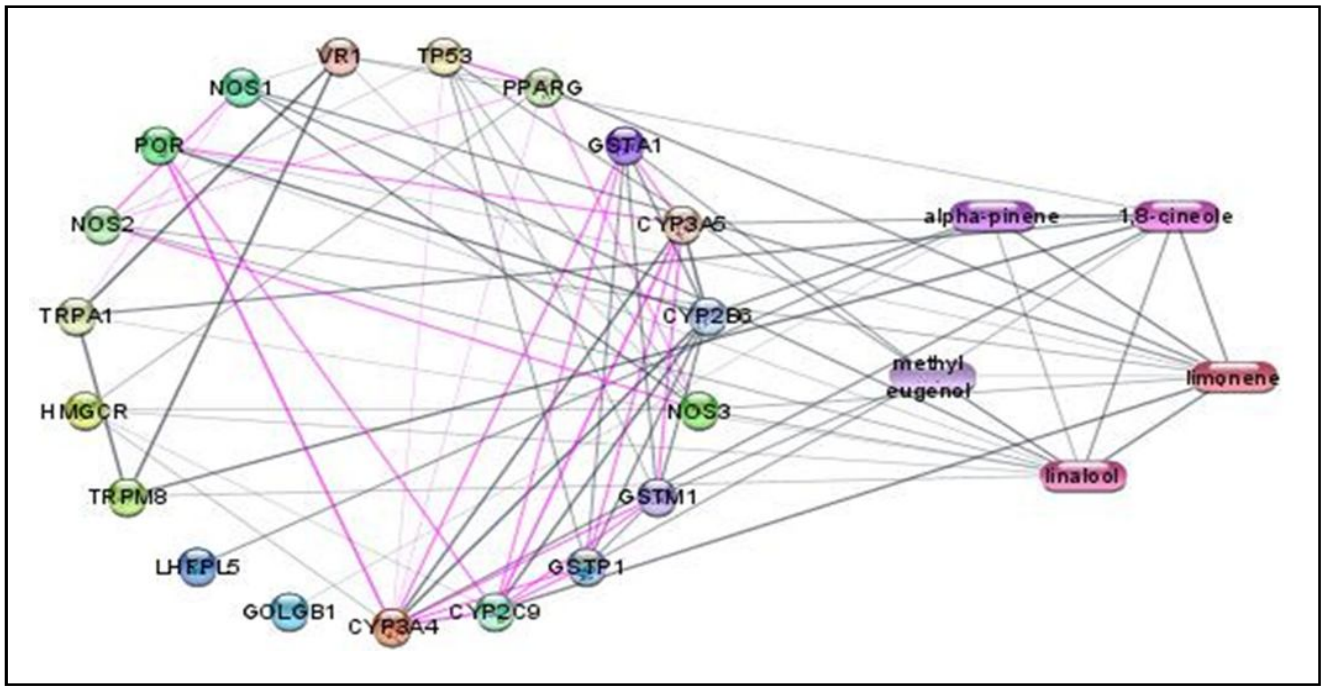

Figure 2: Compound-protein interaction displaying the enhanced interactions with the genes of *T. erecta*.

3.2 Gene ontology analysis

The numerous physiological functions of each gene in the control of pain and other related dysfunction were determined using the Metascape Gene Analysis (metascape.org) tool. The metascape gene analysing tool was used to conduct the research. Each gene was taken from a *Homo sapiens* individual. Furthermore, we evaluated the various physiological functions of each gene in the control of the brain, kidney, lung, and associated disorders using Metascape Gene Analysis (metascape.org), and the network analyst application is used to evaluate a wide range of physiological functions of each gene in the control of heart, kidney, brain, and other illnesses to determine the gene-disease connection. The findings of the analysis have been summarized in Figure 3.

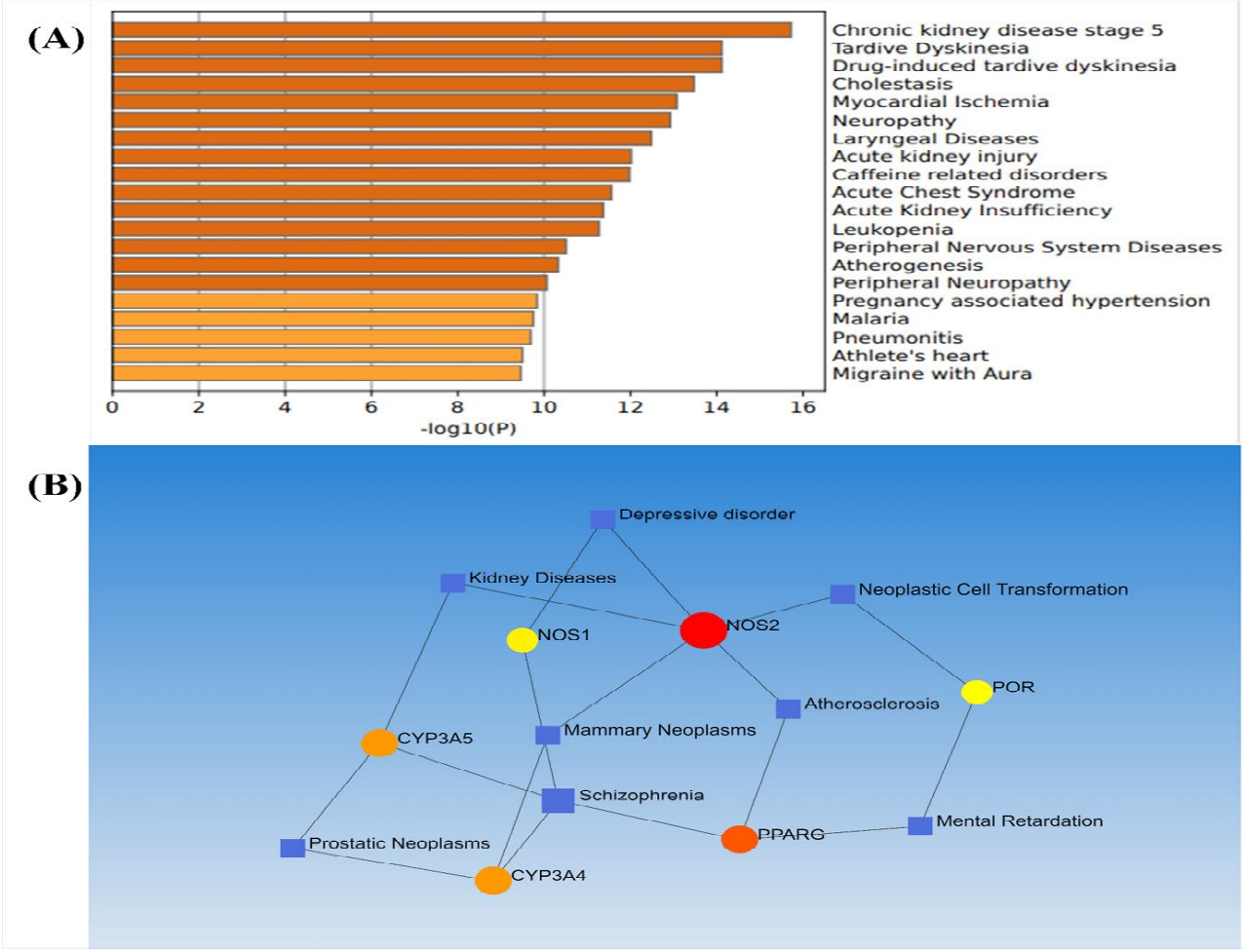

Figure 3: Gene ontology (GO) and gene-disease association network. Figure (A) the GO analysis and (B) showing gene-disease association network.

3.3 *In silico* analysis for determination of the antioxidant activity of *T. erecta*

The *in silico* results shown in Table 2, revealed that *T. erecta* have a strong interaction with 4D1N, with binding values of -6.5 and -5.6 while, methyl eugenol and linalool demonstrated a strong interaction with the binding energy at the sites being -6.5 and -5.6, respectively. The findings of the investigation were compared to the findings of the published article, which revealed that *T. erecta* have a similar binding affinity for 4D1N protein. Aher and Perera's research on the biological interactions of methyl eugenol, linalool, and alpha-pinene found that each chemical had substantial interaction with 4D1N 23, 24.

Table 2: *In silico* docking study of *T. erecta*

S. No.	Compound name	Affinity (kcal/mol)	Dist from rmsd l.b.	Best mode rmsd u.b.	Conventional hydrogen bonding
1.	Limonene	2-6.1	1.282	4.856	TYRD:334
2.	Methyl eugenol	-6.5	0.869	2.830	ARGC:419,SERC:418
3.	Linalool	-5.6	16.584	17.691	TYRB:334, SERC:325
4.	Eucalyptol	-6.1	1.674	3.313	-
5.	Alpha pinene	-5.8	16.747	18.508	-

The influence of the *T. erecta* on antioxidant activity, specifically 4D1N, was determined *via in silico* analysis. The binding affinity of the *T. erecta* with the targeted proteins was calculated using the Autodock tool, where the binding affinity of the *T. erecta* with the corresponding proteins was determined using a traditional hydrogen bond interaction. For each protein, three distinct ligand interaction sites were chosen. The findings of this study revealed that *T. erecta* interactions with 4D1N were strong at each site, with a significant association with the protein. The following result of the study is shown in Figure 4.

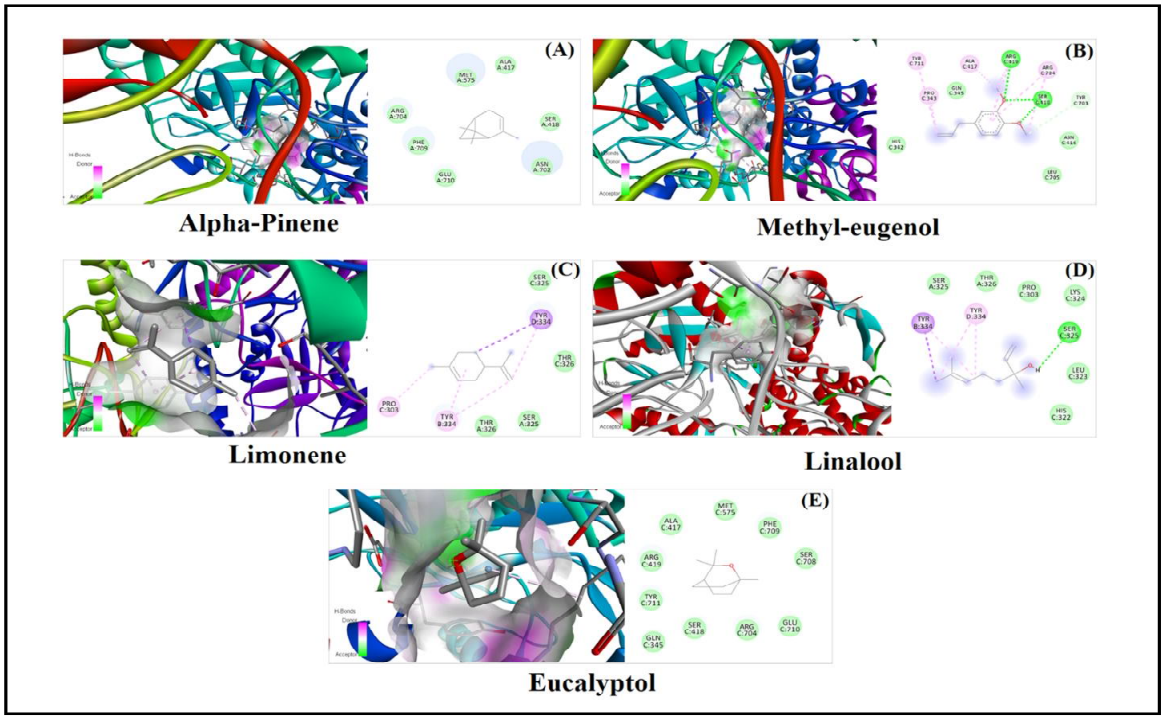

Figure 4: ***In silico*** **molecular docking study between 4D1N (human nNOS heme domain with LArg bound protein) with alpha-pinene, methyl eugenol, limonene, linalool and eucalyptol of** ***T. erecta*****.**

3.4 ADME/TOX analysis

The computational program "Swiss ADME" was used to successfully undertake an ADME/TOX assessment of the *T. erecta*. The ADME, lipophilicity, and drug-likeness response of several chemicals discovered in *Tagetes* were predicted using parameters such as TPSA, consensus Log Po/w, ESOL Log S values, GI absorption, BBB permeant, and log Kp (cm/s) (skin permeation). The fragmental approach TPSA was used to calculate the polar surface area (PSA) of metabolites. Many models and rules use it as a descriptor to estimate some ADME features, particularly absorption and brain access (Daina and Zoete, 2016). The consensus log Po/w represents the lipophilicity of predicted compounds by taking the arithmetic average of five proposed lipophilicity approaches. The partition coefficient among n-octanol and water (log Po/w) is a traditional descriptor for lipophilicity. This area has been dedicated by Swiss ADME due to the vital necessity of physicochemical property assessment for pharmacokinetic drug discovery utilizing computational tools. The models use consensus log Po/w to improve forecast accuracy for physicochemical attributes (Mannhold *et al.*, 2009). The research indicates that a negative logP value for each metabolite indicates that the chemical has a high-affinity hydrophilic character, whereas a positive log P value indicates that the molecule is lipophilic. Similarly, Potts and Guy developed a model that uses the skin permeability coefficient to predict skin permeability (Kp). The lower the log Kp (in cm/s), the less permeant the molecule is to the skin (Daina *et al.*, 2017). Because the log Kp values for all compounds have been less than highly lipophilic. The TPSA (Topological Polar Surface Area) is a fundamental physiochemical measure used to evaluate drug transport characteristics.

Table 3: ADME analysis of screened metabolites from network pharmacology

Molecule	Canonical SMILES	Formula	MW	TPSA	Consensus Log P	GI absorption	BBB permeant	log Kp (cm/s)
Methyl eugenol	C=CCc1ccc(c(c1)OC)OC	$C_1 1H_{14}O_2$	178.23	18.46	2.58	High	Yes	-5.6
Eucalyptol	CC12CCC(CC1)C(O2)(C)C	$C_{10}H_{18}O$	154.25	9.23	2.67	High	Yes	-5.3
Limonene	CC1=CCC(CC1)C(=C)C	$C_{10}H_{16}$	136.23	0	3.37	Low	Yes	-3.89
Linalool	C=CC(CCC=C(C)C)(O)C	$C_{10}H_{18}O$	154.25	20.23	2.66	High	Yes	-5.13
Alpha-pinene	CC1=CCC2CC1C2(C)C	$C_{10}H_{16}$	136.23	0	3.44	Low	Yes	-3.95

Our study revealed that all metabolites have a significant skin permeability with log Kp value of Eucalyptol (-5.3), Limonene (-3.89), Linalool (-5.13), Methyl eugenol (-5.6), and Alpha-pinene (-3.95). The results of the ADME analysis are given in Figure 5 and Table 3.

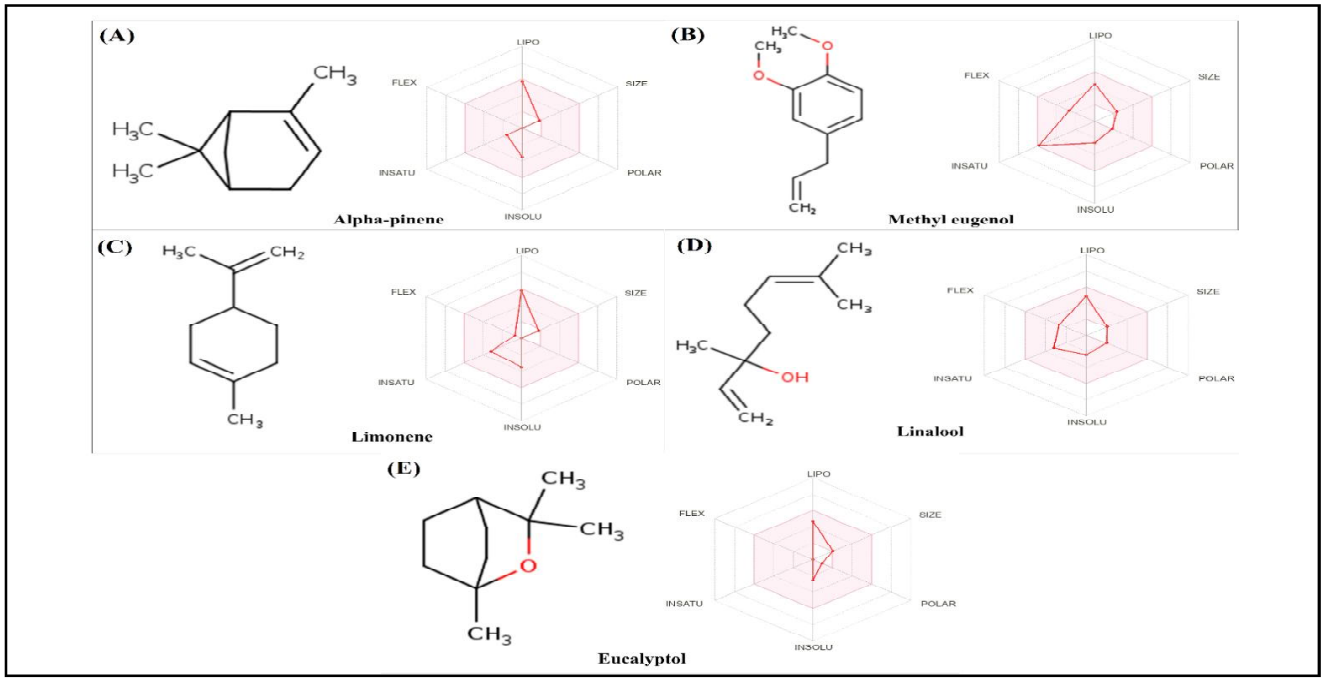

Figure 5: Figure represents the Swiss ADME analysis of selected bioactive compounds of the *T. erecta*, Figure (1) represents chemical structure and the radar plot of alpha-pinene, Figure (2) represents chemical structure and the radar plot of methyl eugenol.

The penetration of the blood-brain barrier (BBB) is exploited for the transmission of centralized active molecules or, in the reverse, for the restricted side effects of vascular medicines. Lipophilicity and apparent polarity are represented by only two physicochemical descriptors (consensus log Po/w and TPSA) (Daina and Zoete, 2016). The predictions for passive BBB penetration, HIA (human gastrointestinal absorption), are given in the radar plots and boiled egg plot of each metabolites have been depicted in Figure 6.

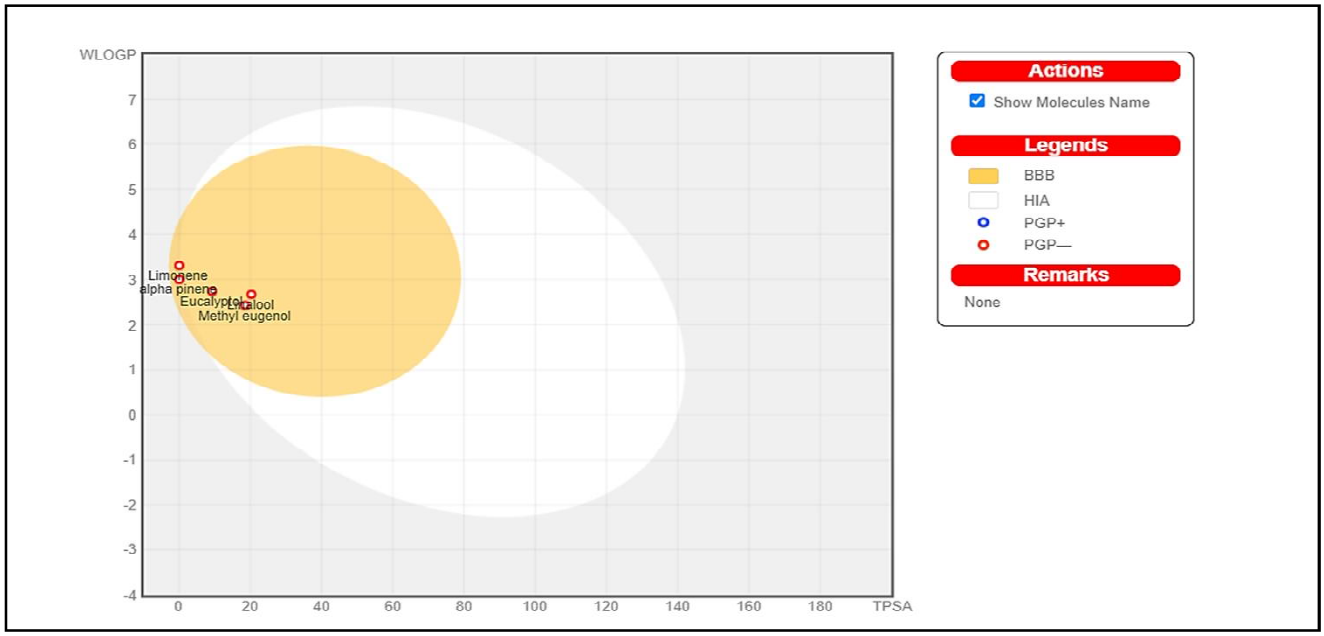

Figure 6: ADME boiled egg plot of *T. erecta* constituents such as methyl eugenol, alpha pinene, linalool, limonene, 1,8-cineole or eucalyptol.

4. Discussion

T. erecta is one of the Indian traditional medical plant which has been exponentially used for alleviating various deleterious diseases. Due to lack of physicochemical and pharmacognostic evidences, the study is associated to investigate the molecular mechanism of *T. erecta* followed by various approaches. Network pharmacology analysis was performed to investigate the molecular mechanism of the metabolites of *T. erecta* identified through GC-MS analysis in our earlier report (Yasheshwar *et al*., 2017). The metabolites were selected and analysed for their biological interaction through the genes involved in oxidative and inflammatory disease and their associated complications. The outcome of the study showed that out of 23 screened metabolites of *T. erecta* only five metabolites were potentially active against the 16 genes which are associated in various pathophysiology induced by the oxidative stress and inflammatory stress. The potential genes such as NOS1, NOS2, CYP3A5, GSTP1, PP53, GSTM1, PPARG, CYP2C9, NOS3, CYP3A4, TRPM8, HMGCP, TRPA1, POR, VR1 and GSTA1 were found interacted with the five metabolites of *T. erecta*. It has been reported that methyleugenol is highly interacted against the inflammation and the oxidative stress induced complication. In a study conducted by Zhou *et al*. (2017) evaluated protective effect of methyleugenol against t-BHP-triggered oxidative injury *via* regulation of various inflammatyory signalling pathways. The outcome of that study showed that methyl eugenol exhibits a protective effect against antioxidative enzymes such as superoxide dimutase (SOD), glutathione (GSH), quinone oxidoreductase (NQO1), as well as the inflammatory cascades proteins such as AMP-activated protein kinase (AMPK), extracellular signal-regulated kinase (ERK) phosphorylation, nuclear factor-erythroid 2-related factor 2 (Nrf2), *etc*., and thus validating the antioxidant and anti-inflammatory effect of methyleugenol (Zhou *et al*., 2017; Choi *et al*., 2010). Linalool has been reported as most prominent antioxidant and anti-inflammatory compounds and thus alleviating their associated complications. In a study reported by Seol *et al*., reported antioxidant activity of linalool which was evaluated in the patients associated with carpal tunnel syndrome. The author reported significant anti-oxidant activity of the linalool against carpal tunnel syndrome induced oxidative stress Seol *et al*. (2016). Furthermore, linalool has been reported for attenuating LPS-induced tumour necrosis-α and well as inflammatory stress *via* regulation interleukin-6 (IL6) using *in vitro* and *in vivo*. The proteins such as IκBα protein, p38, c-Jun terminal kinase were found regulated after treatment of linalool against LPS induced oxidative and inflammatory stress. Gene ontology analysis showed multi-mechanistic and pathophysiological role of the genes found interacted with the genes, revealed that the metabolites regulates oxidative and inflammatory stress induced acute and chronic renal ailments, diabetic nephropathy, positive and negative cellular regulations. Furthermore, it was also found that the metabolites also play an important role (Miguel, 2010).

Furthermore, the targeted metabolites were evaluated for their interaction with the NOSs protein to evaluate the nature of interaction in form of conventional hydrogen bonds. The analysis revealed that out of 5 screened metabolites, methyl eugenol and linalool possessed most prominent interaction with the NOS protein. The previous study has been reported to validate the interaction with the antioxidative enzymes (Gogoi *et al*., 2020; Joshi *et al*., 2021; Li *et al*., 2017; Murakami *et al*., 2017; Varghese *et al*., 2017). In ADME analysis, it was found that the metabolites exhibits high GI absorption, high skin permeabilityas well as blood brain permeability. Hence, the present evidences concludes that the study postulates scientific evidences based on the phytopharmacology of the metabolites present in *T. erecta* play a multi-mechanistic role in the pathophysiology induced by oxidative and inflammatory stress and their associated complications.

5. Conclusion

The study concludes that the metabolites present in *T. erecta* exhibits a protective effect against several acute and chronic pathophysiological morbidities such as acute and chronic renal dysfunction, positive and negative regulations of cellular response, and excretion of toxins, *etc*.,*via* alleviating oxidative and inflammatory stress and thus providing *T. erecta* as an effective medicinal regimen at the glance of naturals.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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