



# Investigation of the Anti-TB Potential of Selected Phytochemicals of *Nigella Sativa* using Molecular Docking Approach

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## **Author's contribution**

The sole author designed, analysed, interpreted and prepared the manuscript.

## **Article Information**

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## **ABSTRACT**

**Background:** Tuberculosis (TB) is one of the foremost causes of human mortality across the world. In general, it is a curable disease and several drugs are available in market for its treatment, however, because of the drug resistance to the currently available anti-TB drugs, the development and/or discovery of new drugs with better efficacy against TB cannot be overlooked. In the present study, we performed virtual screening of the major phytochemicals of the plant *Nigella sativa* for investigating their potential to inhibit some novel drug targets of *Mycobacterium tuberculosis*, which included- pantothenate kinase, type 1 (MtPanK),  $\beta$ -ketoacyl ACP synthase I (MtKasA), and decaprenylphosphoryl- $\beta$ -D-ribose 2'-epimerase 1 (MtDprE1).

**Methods:** The screening of the phytochemicals was investigated through a molecular docking approach using Auto dock vina and the molecular interactions in the protein-ligand complexes were visualized and analysed through PyMol and BioVia Discovery Studio Visualizer.

**Results:** Our *in silico* observations reveal that, out of the nine selected phytochemicals screened, five compounds, namely  $\alpha$ -hederin, dithymoquinone, nigellidine, thymoquinone and thymol binded to one or more of the selected target enzymes with significant docking scores.  $\alpha$ -hederin binded to MtDprE1 and MtKasA with a docking score of  $-8.5\text{kcal/mol}$  and  $-7.9\text{kcal/mol}$ , respectively, dithymoquinone binded to MtKasA, MtDprE1 and MtPanK with a docking score of  $-6.5\text{kcal/mol}$ ,

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–8.2kcal/mol and –9.2kcal/mol, respectively and nigellidine binded to MtDprE1 and MtPanK with a docking score of –8.1kcal/mol and –8.2kcal/mol, respectively. Further, thymol as well as thymoquinone were observed to bind MtKasA with a docking score of –6.6kcal/mol.

**Conclusions:** The results of our study indicate that the five phytochemicals of *N. sativa*, including  $\alpha$ -hederin, dithymoquinone, nigellidine, thymoquinone and thymol, are worth studying further for their anti-TB activity, however, additional biological studies are warranted to validate these findings.

**Keywords:** *Nigella sativa*; tuberculosis; molecular docking; in silico; phytochemicals; *M. tuberculosis*; drugs; drug targets.

## 1. INTRODUCTION

Tuberculosis (TB), an infectious bacterial disease caused by *Mycobacterium tuberculosis* (*M. tuberculosis* or *Mtb*), affects millions of people each year [1]. Being a treatable disease, its treatment is currently available and requires multiple drugs to be taken by the patient at least for six months. However, due to various limitations of the presently available anti-TB drugs and the emergence of drug-resistant strains of *Mtb*, the discovery and development of new drugs against TB are indispensably needed [2,3]. To meet this demand, various anti-TB drug development efforts are being intensively carried out by researchers across the globe and as a result of those continuous efforts a drug development pipeline is currently available, with two new drugs for tuberculosis (delamanid and bedaquiline) already licensed for marketing [4,5]. However, the available drug development pipeline is still not adequate to address TB as a global health issue [3]. Therefore, additional strategies for discovery or development of new anti-TB drugs, are essentially required for overcoming this global health challenge of tuberculosis [2,3]. As natural products of plant origin and plant extracts have been used by humans as traditional remedies for TB management since ancient times. Therefore, one of the promising strategies for anti-TB drug discovery is to test the potential phytochemicals from different plant sources [6-10]. Among the various medicinal plants, *Nigella sativa* (*N. sativa*) is one of the most treasured nutrient-rich herbs with numerous medicinal benefits [11] and recently, the *in vitro* anti-TB activity of *N. sativa* seed extracts and some of its phytochemicals, has been reported in several studies [12-14].

In *M. tuberculosis* there are several enzymes, with important physiological functions, that have been identified as novel drug targets. Here in this study, the three drug-targets/enzymes of *Mtb* including pantothenate kinase, type 1 (MtPanK)[15],  $\beta$ -ketoacyl acyl carrier protein

synthase I (MtKasA) [16], and decaprenylphosphoryl- $\beta$ -D-ribose 2'-epimerase 1 (MtDprE1)[17] were selected, and the major phytochemicals of *N. sativa* were individually screened against each of these enzymes using molecular docking approach. Molecular docking, being a popular tool in virtual screening of small molecules against the protein targets, has been successfully used in several studies investigating the interactions of natural products against specific target proteins [3,18-22]. However, there are no available reports in literature regarding the molecular docking of *N. sativa* phytochemicals towards the selected mycobacterial target enzymes. Therefore, in this *in silico* study, we aimed to target the three selected mycobacterial enzymes and investigated the possible anti-TB potential of the key phytochemicals of *N. sativa*.

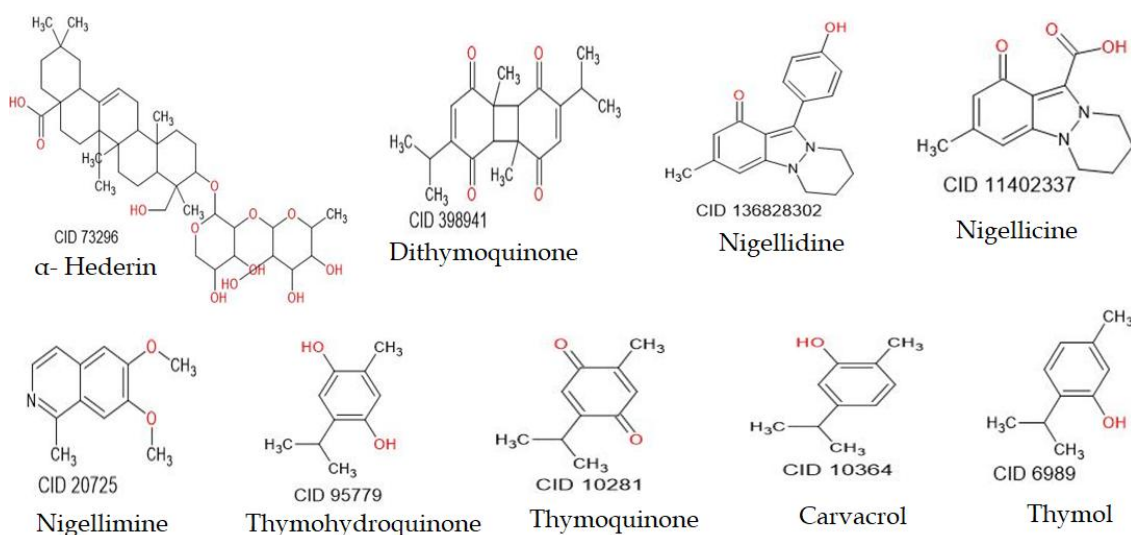
## 2. MATERIALS AND METHODS

### 2.1 Ligand Selection

In this study, the nine chief phytochemicals of the seeds of *N. sativa* and the control inhibitors of the target enzymes, were selected as ligands. The chemical structures and the compound identification (CID) number of the selected phytochemicals of *N. sativa* are shown in Fig.1.

#### 2.1.1 Protein preparation for molecular docking

The crystal structures of MtKasA (PDB ID: 2WGE), MtDprE1 (PDB ID: 4FF6), and MtPanK type 1 (PDB ID: 4BFT) were obtained from the Protein Data Bank (PDB) database (<http://www.pdb.org>). The preparation of the protein structures for molecular docking (which included the removal of the hetero-atoms and water molecules, the addition of polar hydrogens and appropriate charges, and the repair of missing atoms) was performed using UCSF Chimera 1.12 software. The prepared structures were saved in PDBQT format and used as input files during the docking procedure.



**Fig. 1. Chemical structure of the selected phytochemicals of *N. sativa* along with their compound identification (CID) number**

## 2.2 Ligand Preparation

The 3-dimensional (3D) structures of the selected phytochemicals of *N. sativa* were downloaded from PubChem (<https://pubchem.ncbi.nlm.nih.gov/>) and those of the control inhibitors, 2-chloro-N-[1-(5-[[2-(4-fluorophenoxy)ethyl] sulfanyl]-4-methyl-4h-1,2,4-triazol-3-yl) ethyl]benzamide (ZVT), 3-(hydroxyamino)-N-[(1*r*)-1-phenylethyl]-5-(trifluoromethyl)benzamide (OT4), and thiolactomycin (TLM), which are the standard inhibitors for MtPanK, MtDprE1 and MtKasA, respectively, were retrieved from their corresponding PDB entries (<http://www.ebi.ac.uk/thornton-srv/databases/cgi-bin/pdbsum/GetPage.pl?pdbcode=index.html>). All the ligands were prepared for molecular docking using UCSF Chimera 1.12 software. The ligand preparation process mainly included, setting the torsion roots, adding the gasteiger charges, and merging the non-polar hydrogens. The PDBQT files of the prepared ligands were saved and used in molecular docking process.

### 2.2.1 Grid box preparation and molecular docking

Identification of the binding site residues for MtKasA, MtPanK, and MtDprE1 was acquired from the available literature [3, 15-17]. For each receptor protein a grid box covering the active site residues of the protein structure was generated using AutoDock Tools 1.5.7 and the grid box parameters (Table 1) were saved and used as input during the docking procedure. The

molecular docking calculations for all phytochemicals with each of the selected enzymes were performed using AutoDockVina v. 1.1.2 [23]. AutoDockVina results designate the Gibbs free energy of binding ( $\Delta G$  (kcal/mol)) as docking scores which represents the efficacy of ligand binding to chosen receptor [24]. The accuracy of our docking results was validated by re-docking all co-crystallised inhibitory ligands (control inhibitors) into their corresponding protein structures. Further, the docking complexes (protein-ligand complexes) of different poses of the ligands were generated using PyMol molecular graphics system (<https://pymol.org>) [25], and the interactions of the ligands with the selected enzymes were analysed and visualized using PyMol molecular graphics system and BioVia Discovery Studio Visualizer (<https://discover.3ds.com/discovery-studio-visualizer-download>).

## 3. RESULTS

Based on the available literature, here in this study, we screened the chief phytochemicals of *N. sativa* for their possible ability to bind and inhibit the three selected enzymes of *M. tuberculosis*, namely MtKasA, MtPanK, and MtDprE1. The molecular structure of the selected phytochemicals is shown in Fig. 1. The screening was performed by applying an *in silico* molecular docking procedure. For validation of the docking conditions before virtually screening the phytochemicals, each control inhibitor retrieved from its corresponding co-crystallised complex was re-docked against the relevant target

enzyme. After separately docking the phytochemicals with the individual target enzymes, the best pose docking score of each phytochemical towards MtPanK, MtDprE1, and MtKasA was selected and noted (Table 2). The docking score values for each compound were compared to those of the control inhibitors for each target and the phytochemicals with the lowest energy values that are comparable or higher than those of the respective control inhibitors were selected. We observed that  $\alpha$ -hederin, dithymoquinone and nigellidine showed high docking scores/binding affinity towards MtDprE1 (-8.5, -8.2 and -8.1 kcal/mol, respectively), comparable to that of the corresponding control inhibitor, OT4 (-8.3kcal/mol).  $\alpha$ -hederin was also observed to show higher predicted binding towards MtKasA (-7.9 kcal/mol) as compared to that of its control inhibitor, TLM (-6.7kcal/mol). The docking scores of thymoquinone, thymol and dithymoquinone towards MtKasA (-6.6, -6.6,

and -6.5 kcal/mol, respectively) were slightly lower but comparable to that of its control inhibitor (-6.7kcal/mol). Furthermore, the docking scores of dithymoquinone and nigellidine towards MtPanK (-9.2 and -8.2 kcal/mol, respectively) were slightly higher or lower than that of its control inhibitor, ZVT (-8.5kcal/mol) (Table 2).

In order to understand the nature of the inter-molecular bonds between selected phytochemicals and the binding site residues of the corresponding enzyme in the complex, the specific inter-molecular interactions in the docking complexes were visually inspected through PyMol and BioVia Discovery Studio Visualizer. Following the visualization of the different ligand poses in the docking complexes, the best ligand poses were selected and analysed for the interactions between the specific ligand and the active site residues of the associated enzyme as depicted in Figs. 2-4.

**Table 1. Grid parameters (dimensions in X, Y, Z-axis) for the selected target enzymes**

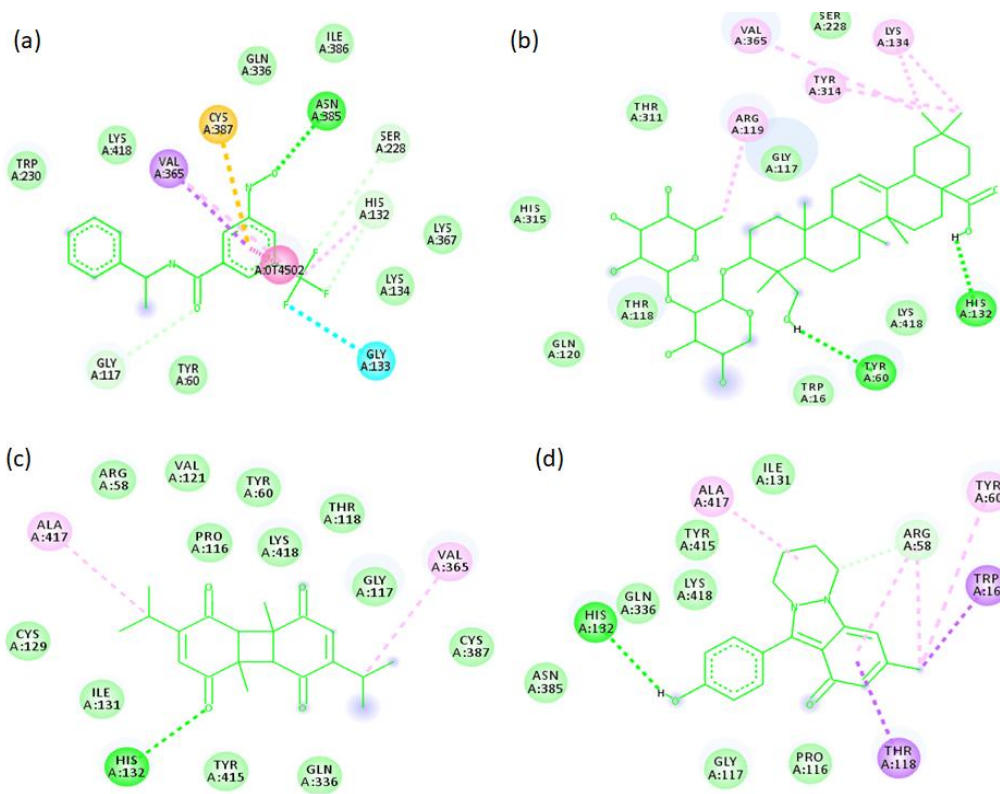
Target Enzyme	Centre Grid Box dimensions	Size Grid Box dimensions
MtPanK (PDB ID: 4BFT)	-20 × -5 × 10	30 × 30 × 30
MtDprE1 (PDB ID: 4FF6)	14.99 × -20.507 × 37.226	45 × 40 × 35
MtKasA (PDB ID: 2WGE)	33.8 × 0.5 × -4.5	48 × 48 × 55

Abbreviations: MtDprE1; decaprenylphosphoryl- $\beta$ -D-ribose 2'-epimerase 1 of Mtb, MtKasA;  $\beta$ -ketoacyl ACP synthase I of Mtb and MtPanK; pantothenate kinase, type 1 of Mtb

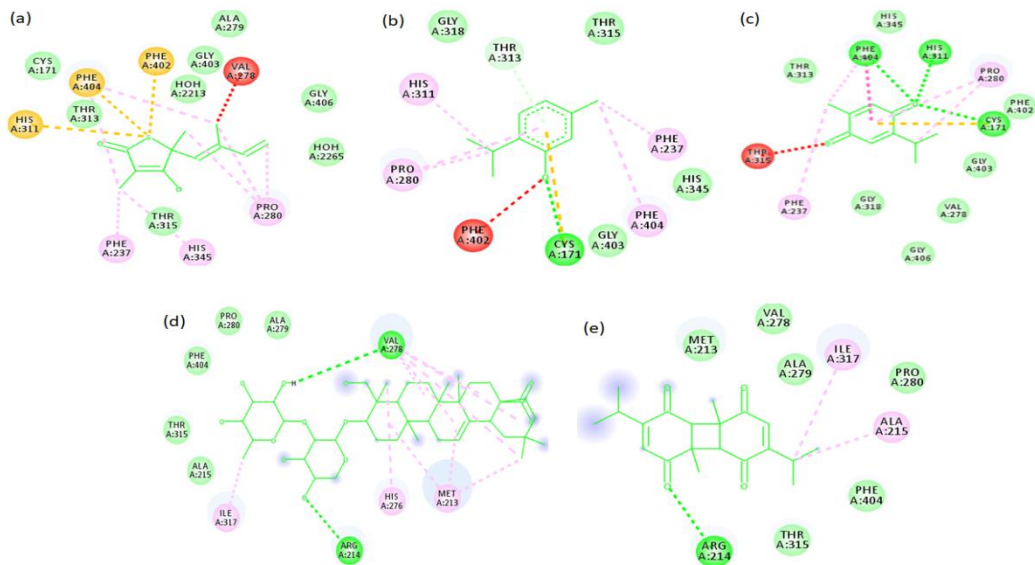
**Table 2. Predicted binding affinity (represented as docking scores in kcal/mol) of the main phytochemicals of *N. sativa* and the control inhibitors against *M. tuberculosis* target enzymes**

(Control inhibitors or Phytochemicals of <i>N. sativa</i> )	Docking scores against the selected target enzymes		
	MtDprE1 (PDB ID: 4FF6)	MtKasA (PDB ID: 2WGE)	MtPanK (PDB ID: 4BFT)
Control inhibitors			
OT4	-8.3	ND	ND
ZVT	ND	ND	-8.5
TLM	ND	-6.7	ND
Phytochemicals of <i>N. sativa</i>			
$\alpha$ -hederin	-8.5	-7.9	-6.7
Nigellidine	-8.1	-5.9	-8.2
Dithymoquinone	-8.2	-6.5	-9.2
Nigellicine	-6.8	-5.9	-6.8
Carvacrol	-5.7	-6.0	-5.6
Nigellimine	-5.7	-5.1	-5.6
Thymohydroquinone	-5.7	-6.0	-5.7
Thymol	-5.6	-6.6	-5.5
Thymoquinone	-5.9	-6.6	-6.0

Abbreviations: MtDprE1; decaprenylphosphoryl- $\beta$ -D-ribose 2'-epimerase 1 of Mtb, MtKasA;  $\beta$ -ketoacyl ACP synthase I of Mtb, MtPanK; pantothenate kinase, type 1 of Mtb, OT4; 3-(hydroxyamino)-N-[(1R)-1-phenylethyl]-5-(trifluoromethyl)benzamide, ZVT; 2-chloro-N-[1-(5-{[2-(4-fluorophenoxy)ethyl] sulfanyl}-4-methyl-4h-1,2,4-triazol-3-yl) ethyl]benzamide, TLM; Thiolactomycin, and ND; not determined.

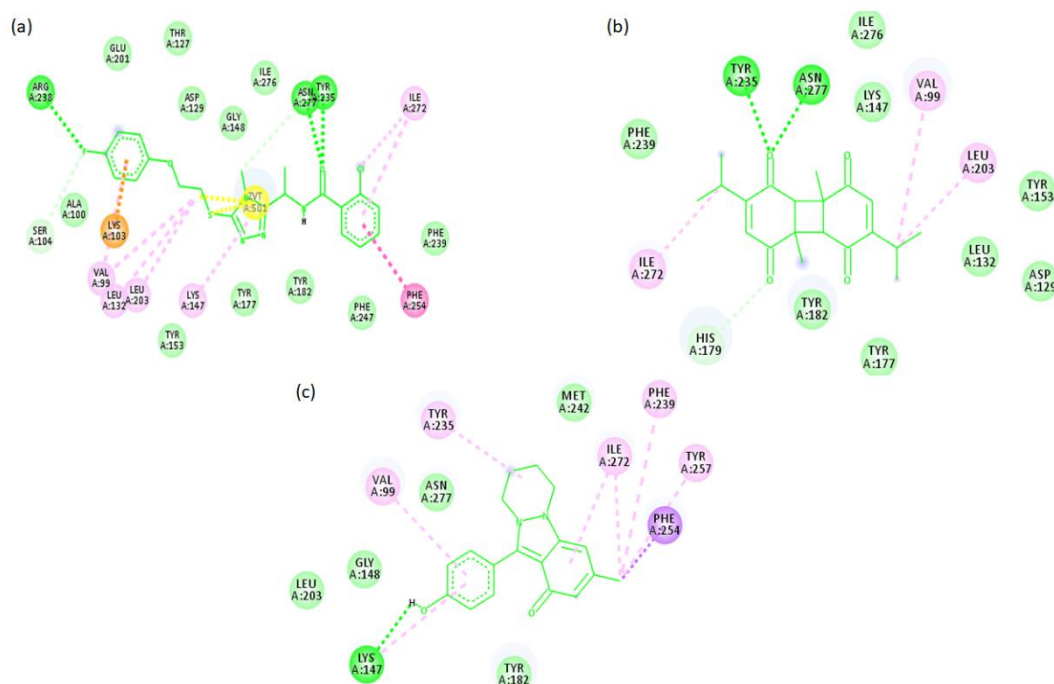


**Fig. 2. 2D representation of the interaction of ligands with amino acid residues in the active site of MtDprE1; (a) Control inhibitor, 0T4, (b)  $\alpha$ - hederin, (c) Dithymoquinone, (d) Nigellidine.** The dotted lines in different colours indicate the types of interaction of the ligand with the amino acid residues in the active site of the target enzyme (dark green; hydrogen bonds, light green; Van der Waals, dark purple or dark pink; Pi-Sigma, light pink; Pi-Alkyl, Cyan; Halogen (Fluorine) and yellow; Pi-Sulfur interactions).



**Fig. 3. 2D representation of the interaction of ligands with amino acid residues in the active site of MtKasA; (a) Control inhibitor, TLM, (b) Thymol, (c) Thymoquinone, (d)  $\alpha$ - hederin, (e) Dithymoquinone.**

The dotted lines in different colours indicate the types of interaction of the ligand with the amino acid residues in the active site of the target enzyme (dark green; hydrogen bonds, light pink; Pi-Alkyl, dark red; unfavourable donor-donor, dark pink; Pi-Sigma and yellow; Pi-Sulfur interactions).



**Fig. 4. 2D representation of the interaction of ligands with amino acid residues in the active site of MtPanK; (a) Control inhibitor, ZVT, (b) Dithymoquinone, (c) Nigellidine.**

The dotted lines in different colours indicate the types of interaction of the ligand with the amino acid residues in the active site of the target enzyme (dark green; hydrogen bonds, dark purple or dark pink; Pi-Sigma, light purple or light pink; Pi-Alkyl, yellow; Pi-Sulfur, light green; Van der Waals interactions).

The phytochemical  $\alpha$ -hederin interacted with the binding residues of MtDprE1 (Fig. 2b) and MtKasA (Fig. 3d) through two hydrogen bonds each. The other two phytochemicals, nigellidine and dithymoquinone interacted with the binding residues of MtDprE1 through one hydrogen bond each (Fig. 2c and d), and with the binding residues of MtPanK through 2 and 1 conventional hydrogen bonds, respectively (Fig. 4b and c). Further, thymol, thymoquinone and dithymoquinone interacted with MtKasA through 1, 3 and 1 conventional hydrogen bonds, respectively (Fig. 3b, c and e). In addition to the conventional hydrogen bonds, some non-covalent interactions (like Pi-Alkyl interactions, Pi-Sigma interactions etc.) were also observed between these top-ranked *N. sativa* phytochemicals and the active site residues of the corresponding docked enzymes, as depicted in the two-dimensional (2D) illustrations (Figs. 2-4). The molecular interaction of various active site residues of MtDprE1, MtKasA and MtPanK with their respective control inhibitors is available in the literature [3] and reported here as well (Figs. 2a, 3a and 4a). Based on our observations, we

here report that  $\alpha$ -hederin, thymoquinone, dithymoquinone, thymol and nigellidine possess the ability to bind and inhibit one or more of the selected enzymes of *Mtb* and are worth investigating further for their anti-TB efficacy under *in vitro* and *in vivo* models.

#### 4. DISCUSSION

In this study, the *in silico* binding affinity of the main phytochemicals of *N. sativa* towards the three mycobacterial enzymes, including MtKasA, MtDprE1 and MtPanK was investigated. The reason for selecting these proteins is that they are among the key enzymes required for the growth and survival of *Mtb* within the eukaryotic host. Several vital pathways of *Mtb*, such as cofactor biosynthesis, cell wall biogenesis and signal transduction are regulated by these enzymes and their absence in mammalian cells makes them highly selective drug targets for TB. In addition, these enzymes represent some emerging drug-targets against which no confirmed drug is presently available [15–17]. Although several *in silico* studies have reported

the possible inhibitory potential of various *N. sativa* phytochemicals against SARS-Cov-2 [26-32], the anti-mycobacterial potential of *N. sativa* constituents has been reported in a few studies only [12-14]. In this preliminary study, the nine prominent phytochemical compounds of *N. sativa* were selected and their inhibitory potential against the three selected mycobacterial enzymes was investigated through *in silico* molecular docking. In molecular docking, scoring algorithms are used to estimate the likelihood of a given compound to bind a protein target. Among the nine compounds, five ( $\alpha$ -hederin, dithymoquinone, nigellidine, thymol and thymoquinone) were observed to bind one or more selected target enzymes with significant binding energies/docking scores, higher or comparable to those of the control inhibitors of the corresponding enzymes (Table 2). Based on our docking results, the best predicted-binders to MtDprE1 included  $\alpha$ -hederin, dithymoquinone and nigellidine, among which dithymoquinone and nigellidine also bind to MtPanK with a good binding affinity. The best predicted-binders to MtKasA included  $\alpha$ -hederin, dithymoquinone, thymol and thymoquinone (Table 2).

Further, after visualizing the docked complexes using PyMol, it was observed that like the control inhibitors, the selected phytochemicals with significant docking scores bind within the binding pocket in the target proteins (Figs.2-4). The top five compounds ( $\alpha$ -hederin, dithymoquinone, nigellidine, thymol and thymoquinone), among the nine selected phytochemicals, efficiently bind to the binding pocket of one or more target enzymes and stably interacted with the interacting residues in the active site (Figs. 2-4). The interaction involved various bonds (including, conventional hydrogen bonds, Pi-Alkyl, Pi-Sigma bonds etc.) which might lead to the possible inhibition of activity of the specific target enzyme. On the basis of the findings of our study, we suggest that the phytochemicals  $\alpha$ -hederin, dithymoquinone, nigellidine, thymol and thymoquinone are worth studying further through *in vitro* biological evaluation.

## 5. CONCLUSION

In the current study, a molecular docking approach was applied to identify potential anti-TB compounds from the selected phytochemicals of *N. sativa*. Based on their docking score and stable interactions with one or more selected drug targets of *Mtb*, five phytochemicals-dithymoquinone,  $\alpha$ -hederin, nigellidine, thymol

and thymoquinone of *N. sativa* were identified and hypothesized as possible inhibitors of *Mtb*. However, further biological evaluations are essential to establish their comprehensive pharmacological role.

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## COMPETING INTERESTS

Author has declared that no competing interests exist.

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