

Phytochemicals from *Alangium salvifolium* (Alangiaceae): Structures, Molecular Docking and Antioxidant Activity

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Phytochemicals from *Alangium salvifolium* (Alangiaceae): Structures, Molecular Docking and Antioxidant Activity

Abstract

7 Objectives: The current study aimed at retrieve and draws the secondary metabolite structure of *Alangium salvifolium* and assessing its anti-oxidant and ROS elimination activities. Methods: retrieve/draws of the compounds were carried out using *chem.-sketch* software. The 3-D structures of the Phytochemicals compounds were visualized based on the UV, NMR spectral data along with their mass-spectrometric analyses. The antioxidant and ROS elimination activity were evaluated *in-silico* using the ACD labs, **7** Rx, RASMOL, PYMOL, Aragslab and Discovery studio. Key findings: Phytochemicals structure drawing of *A.salvifolium* resulted in the structured and identification of five phytochemicals. The plant phytochemicals showed significant anti-oxidant enzymes activity enhancer and ROS eliminator through blocking to its ROS generation receptor. Conclusion: phytochemicals were drawing from *A. salvifolium*. To the best of our knowledge, among these phytochemicals, were studied anti-oxidant enzymes metals binding doain to increase the ROS scavenging activity for the first time from in-silico study with molecular docking. Moreover, study of phytochemicals simulation was for the first time from this plant. The plant revealed promising increase the antioxidant activities virtual screening. This gives rationale to some of its pharmacological properties and suggests additional antioxidant effects, for as a scavenger as well as anti-oxidant enzyme stimulator, which have not been reported yet.

Key words:- *Alangium salvifolium*, Phytochemicals, molecular docking study, ROS elimination activity

INTRODUCTION

11 Phytochemical compounds are found in plants that are not required for normal functioning of the body, but have a beneficial effect on health or play an active role in amelioration of diseases. The effectiveness phytochemicals in the treatment of various diseases may lie in their antioxidant effects (Akinmoladun *et al.*, 2017). Oxygen is an element obligatory for life; living systems have evolved to survive in the presence of molecular oxygen and for most biological systems. Oxidative properties of oxygen play a vital role in diverse

biological phenomena. Oxygen has double-edged properties, being essential for life; it can also aggravate the damage within the cell by oxidative events (Shinde, *et al.*, 2006).

³ *Alangium salvifolium* wang belongs to the family of Alanginaceae. Ankola and Alangi are its common name in India, and Stone Mango in English. It is a small deciduous thorny tree or shrub (Uthiraselvam *et al.*, 2012) which is distributed in tropical and subtropical region such as Bangladesh, India, China Phillipines, Africa, Srilanka and Indochina (Ronok *et al.*, 2013). An array of ailments including diabetes, jaundice, gastric disorders, protozoal diseases, rheumatic pain, burningsensation, haemorrhages, lung cancer, poisonings, leprosy and many inflammatory patches have been treated by using various parts of the plant (Meera *et al.*, 2013). Many bioactive phytochemicals such as several flavanoids, phenolic compounds, irridoid glycosides and oxyoglucosides have been isolated by phytochemical screening of it (Gopinath, 2013). Literature review of the plant indicates the presence of coumarins, triterpenoids, and some potent alkaloids in it (Savithamma *et al.*, 2012). ⁵ Plant derived antioxidants play a very important role in alleviating problems related to oxidative stress. The antioxidant property of isolated from was established on streptozotocin-induced diabetic Wister rats. Administration of either Costunolide (20 mg/kg) or Eremanthin (20 mg/kg) for 60 days caused a significant increase in enzymatic activity of SOD, CAT and GPx, when compared with untreated ¹⁴ ³ Moreover, maximum antioxidant potential, including DPPH radical scavenging (IC₅₀: 11.26±1.29 µg/ml), FRAP (EC₅₀: 26.64±2.17 µg/ml) and TAC (639.55±10.51 mg/g ascorbic acid) was found in the CASR. Donepezil. ⁵ To best of our knowledge, the receptor-level mechanism behind this process is no where mentioned. ⁵ Present study was aimed at the analysis of receptor-level binding affinity of secondary metabolites of *Alangium salvifolium* with SOD, CAT and GPx through molecular docking.

² METHODS

I. Structure retrieval

a. The protein data bank (PDB): The structure homologues for elastin and collagen protein

Sequence query was retrieved in PDB.

- b. The research laboratory for structural bioinformatics (RCSB): The molecular shape of elastin and collagen was retrieved from RCSB PDB (PDB – www.rcsb.org/).
- c. PDB sum: The PDBsum ([PDBsum–www.ebi.ac.uk/pdbsum/](http://www.ebi.ac.uk/pdbsum/)), a pictorial database that provides an at-a-glance overview of the contents of each 3D structure deposited in the Protein Data Bank(PDB) was used to get the 3-D structure of elastin and collagen.
- II. Structure visualization–RASMOL: RasMol ([RasMol–www.rasmol.org/](http://www.rasmol.org/)), a molecular graphics program intended for the visualization of proteins, used for structural visualization of elastin and collagen.
- III. Three dimensional structure of inhibitors-CHEMSKETCH: The Chemical structure of Withaferin-A.([Chem Sketch–www.acdlabs.com/download/](http://www.acdlabs.com/download/)), a quite powerful chemical structure drawing program.
- IV. Docking: Docking was done with the PyRx software ([pyrax–www.pyrxviana.com/](http://www.pyrxviana.com/)), in which the result is being obtained on the basis of pose energy. Docking calculations attempt to place 'Ligand into Binding Sites'. The binding affinity was expressed kcal/mol. The atoms that make up the Ligand like inhibitor, and the Binding Site on the protein where the inhibitors bind the Structure were drawn in Discovery studio 2.1 version.

RESULTS & DISCUSSION

The SOD, CAT and GPx x-ray crystallography structure proteins were retrieved and analyzed and it was docked to phytochemical compounds from *A. salviolium*. The results are presented as follow:

I. Retrieving three dimensional structures of anti-oxidant enzymes.

The structure of antioxidant enzymes (AE) SOD, CAT, and GPx with PDB Id: 1WB8, 1JKU, 106D were as taken for further analysis. This structure was analyzed to know details of the AE molecule. The secondary structure information about AE proteins have been retrieved from PDB sum database. The topology of the different secondary structures of AE and the amino acid residue in which each helices and sheets are formed. The three-dimensional structures of AE are composed of similar α/β TIM barrels. The symmetry of the TIM barrel is disrupted by the presence of two short antiparallel β -strands at the N-terminus connected by a tight turn closing the bottom of the barrel (El-Kabbani et al., 1998). The PDB file was downloaded and viewed in

RasMol and their various models are given in table-1 Fig. 1a, b,c.

II. Binding site prediction – Q-SiteFinder

The protein structure of AE was given as input to QSiteFinder tool and binding site of the protein was predicted. Ten best 'binding sites' were predicted. The amino acids and the atoms involved in the site were listed

III. Drawing three dimensional structures of inhibitors-

CHEMSKETCH (ACD labs)

The chemical structure of the following *A. salvifolium* APIs collected from literatures were drawn in ChemSketch and visualise into 2D and 3D dimensional structures and its general properties were summarized in table-2 Fig. 2.

IV. Making legends pharmacophore by using of ArgusLab:

Ligands energy level and its simulation properties were assess by using of Argus Lab software. Various energy level calculation and visualization was summarized in table -3 and fig3.

V. Docking (AUTODOCK-viana):

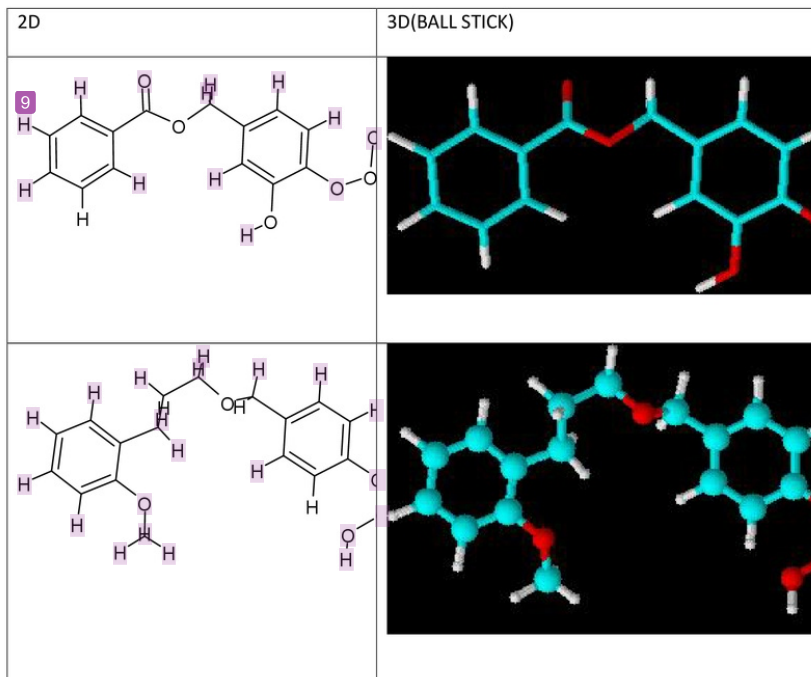
Using PyRx 2.9 version, the receptor, AEs.pdb file and the ligand pdb file were taken and the protein side chain molecules were removed with the help of various tool controls for their perfect visualization. Hetero atoms were removed and the molecule was used for docking. The binding site molecules were stored as separate PDB file and that was used for the analysis. Then, the protein file and the ligand pdb file were loaded and docking studies were performed. The best docked conformation with its binding energy was found and details are given below Table-3. While performing docking the protein and ligand appeared in a grid as shown below and the various binding configurations are analyzed and finally the list of number poses are given as output and saved as .SDF files.

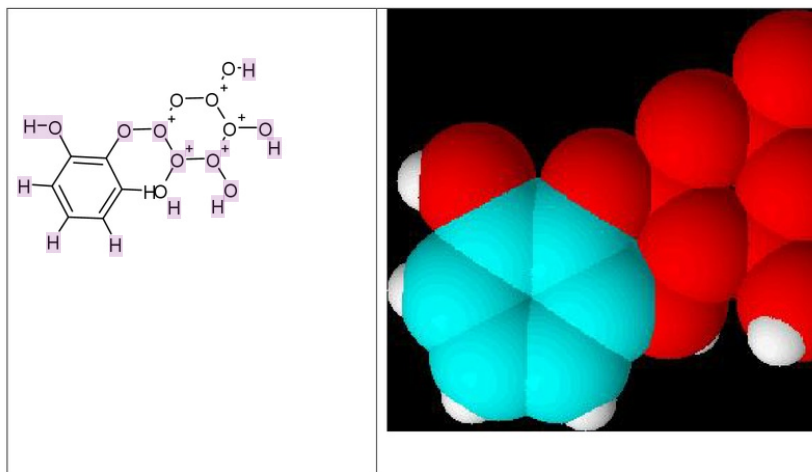
Hydrogen bonds were added and energy was minimized using CHARMM force field. Further, docking studies also carried out using Discovery studio 3.1 version. The details are given in Fig. 4,5, 6.

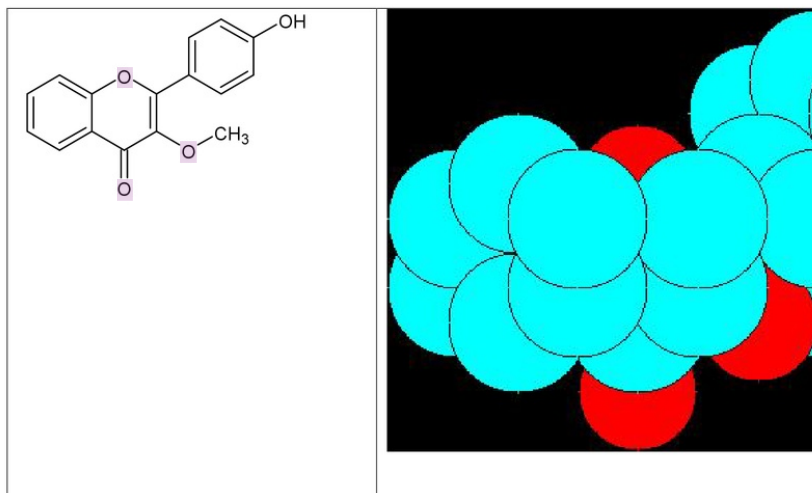
The *A. salvifolium* phytochemicals effectively docked in to the binding site of AEs protein indicating that they are efficient drug compounds. All these binding ligands viz., 4(benzoyloxy)methyl-2hydroxyphenoxy tetrahydroxy hexoxone 1,2,3,4,5, pentaum Tetahydroxy(2hydroxy phenoxy)hexone 1,2,3,4,5 pentaum, Tetahydroxy(2hydroxy phenoxy)hexone 1,2,3,4,5 pentaum showed efficient docking as indicated by binding energy and all are efficient inhibitors.

Table no.A:- General Properties of phytochemicals obtained from *Alangium salvifolium*

s.no.	properties	Alangium 1	Alangium 2	Alangium 3	Alangium 4
1	Name of chemicals	4(benzoyloxy)methyl-2hydroxyphenoxy tetrahydroxy hexoxone 1,2,3,4,5, pentaum		Tetahydroxy(2hydroxy phenoxy)hexone 1,2,3,4,5 pentaum	Tetahydroxy(2hydroxy phenoxy)hexone 1,2,3,4,5 pentaum
2	Molecular formula	C ₁₄ H ₁₅ O ₁₄	C ₁₇ H ₂₃ O ₁₂	C ₆ H ₉ O ₁₂	C ₁₆ H ₁₂ O ₄
3	molecular weight	407.26	419.36	273.13	268.26
4	Composition				
5	Molar refractivity	81.88	94.46	46.12	76.43





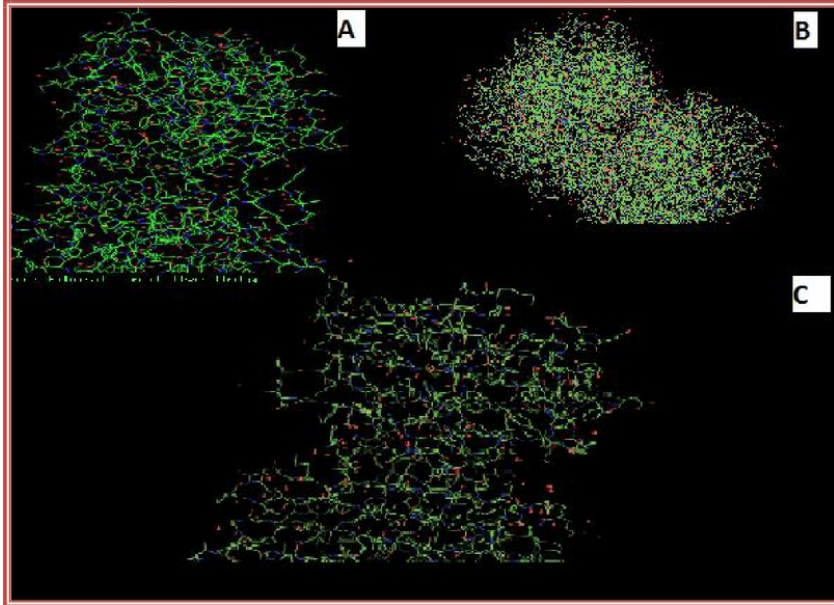


chemical structures of *Alangium salvifolium* Phytochemicals obtained from Chem-Sketch(2D,3D)

sno	Protein name	PDB ID	Protein code	No of chain	Total amino acids
9	GPX	106D		2	370
10	catalyse	1JKU		8	1918
8	SOD	1WB8		6	302

Table1- protein (Receptor) general information

Figure1:- protein 3D structure(A GPx,B CATALASE,C SOD)



Figure;-2 Energetic structure of ligand

LIGAND	HIGEST OCCUPIED	LOWEST UNOCCUPIED	ESP-MAPPED
ALANGIUM 1			
ALANGIUM 2			
ALANGIUM 3			

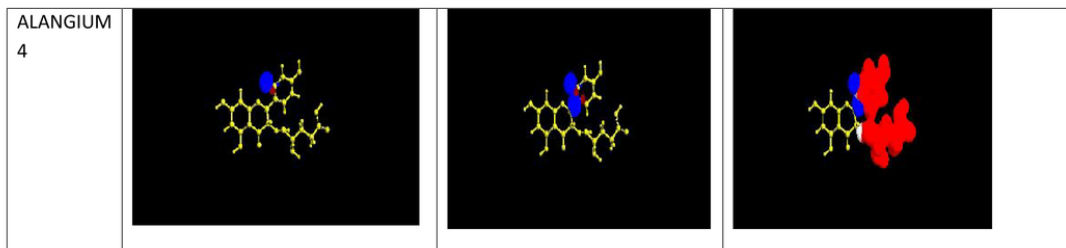


TABLE-2 ligand energy related specification (argus lab result)

S.NO	Specification	Alangium 1	Alangium 2	Alangium 3	Alangium 4
1	SCF energy	-231.767296889	-300.7076472584	47.3947768704	213.3165388741
2	Geometry	231.819691035	-300.771772957	47.521422858	213.325870339sss

Table 3. Mean values of docking energies (kcal/mol) and standard deviation for each skeletal type of *Alangium salvifolium* phytochemicals as ligands with anti-oxidant enzymes enzyme targets.

target	ligands	Dimession Centre (x=25Ay=25z=25	No of pose	RSD %lower	RSD %upper	Mean binding

SOD	Alangium 1	X=16.0161, Y=70.1678, Z=15.4010	9	114.74%	57.7%	-7.6
	2		9	52.72%	57.72%	-7.0
	3		9	103.74%	89.09%	-6.3
	4		9	42.62%	39.74%	-7.4
CAT	1	X= 48.8446 y= 101.718 z=38.2861	9	61.17%	54.60%	-8.9
	2		9	49.96%	51.85%	-8.3
	3		9	72.23%	67.91%	-6.7
	4		9	47.92%	45.56%	-8.1
gpx	1	X=-12.041 y=22.8816 Z=9.2389	6	75.32%	78.04%	-7.1
	2		4	79.61%	68.17%	-4.7
	3		9	151.01%	122.16%	-5.5
	%4		6	56.07%	61.34	-4.4

target	ligands	Dimession Centre (x=25Ay=25z=25)	No of pose	RSD %lower	RSD %upper	Mean binding
SOD	Alangium 1	X=16.0161, Y=70.1678, Z=15.4010	9	114.74%	57.7%	-7.6
	2		9	52.72%	57.72%	-7.0
	3		9	103.74%	89.09%	-6.3
	4		9	42.62%	39.74%	-7.4
CAT	1	X= 48.8446 y= 101.718 z=38.2861	9	61.17%	54.60%	-8.9
	2		9	49.96%	51.85%	-8.3

	3		9	72.23%	67.91%	-6.7
	4		9	47.92%	45.56%	-8.1
gpx	1	$X=-12.041$ $y=22.8816$ $Z=9.2389$	6	75.32%	78.04%	-7.1
	2		4	79.61%	68.17%	-4.7
	3		9	151.01%	122.16%	-5.5
	%4		6	56.07%	61.34	-4.4

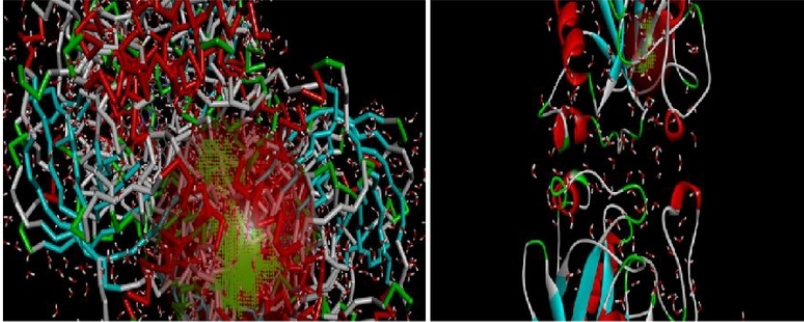


Figure-3

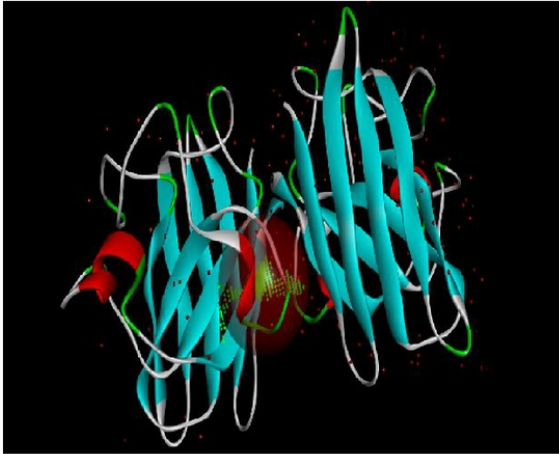


Fig.4. ALANGIUM (spherical & mesh ⁵ model) docked with the active site of SOD, CAT and GPX

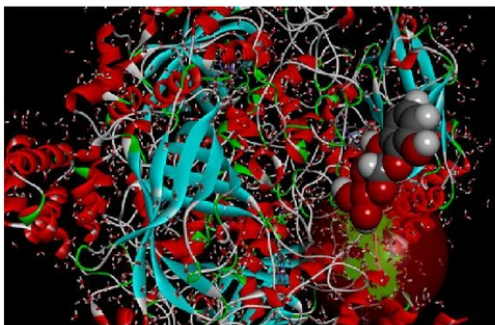
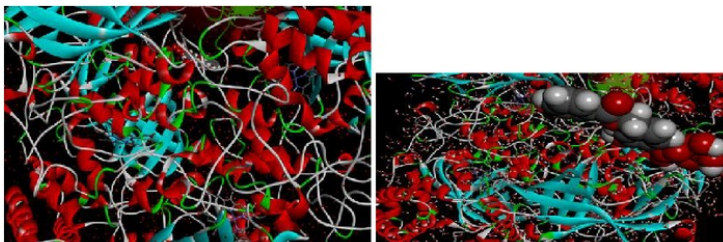
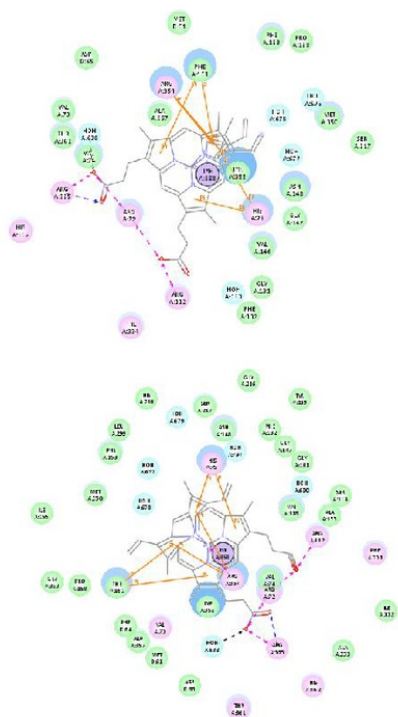


Fig 5: ALANGIUM phytochemicals bound with the pocket of SOD,CAT GPX metal domain (CPK) of the receptor ⁵ bound exactly with metal site domain of receptor.



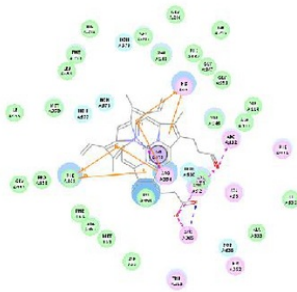
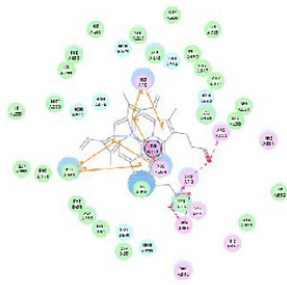


Fig-6(2D DIAGRAM)The receptor-ligand interaction details of ALANGIUM

Discussion

Antioxidant enzymes are capable of stabilizing, or deactivating free radicals before they attack cellular components. They act by reducing the energy of the free radicals or by giving up some of their electrons for its use, thereby causing it to become stable. In addition, they may also interrupt with the oxidizing chain reaction to minimize the damage caused by free radicals. For the past decade, countless studies have been devoted to the beneficial effects of antioxidant enzymes(Warigton enzyme manual2009) .The superoxide dismutases (SOD) are a major cellular defense system against superoxide in all vascular cells. These enzymes contain redox metals in the catalytic center and dismutase superoxide radicals to hydrogen peroxide and oxygen. Three different isoforms of SOD have been identified: the mitochondrial manganese-containing SOD (MnSOD, SOD-2), the cytosolic copper/zinc-containing SOD(CuZnSOD, SOD-1), and the extracellular SOD (ecSOD, SOD-3), which is also a copper/zinc-containing enzyme that is mainly produced and secreted by VSMC and binds to glycosaminoglycans in the vascular extracellular matrix on the endothelial cell surface. Glutathione peroxidase (GPX) is a selenium-containing antioxidant enzyme that effectively reduces hydrogen peroxide and lipid peroxides to water and lipid alcohols, respectively, and in turn oxidizes glutathione to glutathione disulfide. In the absence of adequate GPX activity or glutathione levels, hydrogen peroxide and lipid peroxides are not detoxified and may be converted to hydroxyl radicals and lipid peroxy radicals, respectively, by transition metals (eg, Fe²⁺). The GPX/glutathione system is thought to be a major defense in low-level oxidative stress. Catalase Catalase is an intracellular antioxidant enzyme that is mainly located in cellular peroxisomes and to some extent in the cytosol, which catalyzes the reaction of hydrogen peroxide to water and molecular oxygen in a 2-step reaction involving compound I. By removing hydrogen peroxide, it indirectly detoxifies superoxide radicals, which are turned into hydrogen peroxide by SOD. The enzyme also has peroxidase activity and reacts with organic peroxides and hydrogen donors to water and organic alcohols. Catalase is very effective in high-level oxidative stress and protects cells from hydrogen peroxide produced within the cell. The enzyme is especially important in the case of limited glutathione content or reduced GPX activity and plays a significant role in the development of tolerance to oxidative stress in the adaptive response of cells. Abundant evidence implicates antioxidant enzymes as important components of lung defense after oxidative stress. Many of these enzymes appear to be regulated independently at the molecular level although coordinate increases in biosynthesis and activity levels of some enzymes are observed under certain situations. Undoubtedly, the balance between levels of enzyme induction and the magnitude or extent of oxidant injury to lung determines the outcome of biological responses which may include either adaptation to oxidative stress or lung injury. Endogenous baseline levels of antioxidant enzymes in various lung cell types may also be

important in susceptibility to oxidant-induced cell damage as high levels of constitutive enzymes may preclude inducibility. Although heterogeneous effects are observed in many situations, a common denominator of several stresses (hyperoxia, paraquat, mineral dusts) is increases in expression of MnSOD. Alleviation of paraquat (26) and asbestos-induced (27) cell damage after transfection of genes encoding MnSOD into cells in vitro suggest a causal relationship between induction of this enzyme and prevention of cell death. That increased expression of MnSOD can serve as a biomarker of chronic inflammation or lung disease or a biosensor of oxidant stress is suggested by recent work in this laboratory showing elevated steady-state mRNA levels of MnSOD in cells from bronchoalveolar lavage of rats exposed to asbestos by inhalation (manuscript in preparation). Increases in mRNA levels occur in a dosage-dependent fashion directly related to the airborne concentrations of dusts. In addition to the well-recognized antioxidant enzymes discussed in this review, a number of other antioxidants exist in the lung both intracellularly and extracellularly. These include substances in epithelial cell lining fluid, ceruloplasmin, heme oxygenase, and glutathione. Recent data suggest that the relative importance of these antioxidant sources may vary with the type and degree of oxidant stress. For example, in human mesothelial cells (26) the glutathione redox cycle plays an important role in detoxifying low levels of oxidants, with catalase providing protection against severe oxidant stress. The cloning of genes encoding antioxidant enzymes and the development of shuttle vectors enabling overexpression of these enzymes in cells in vitro are exciting recent findings with implications for gene therapy. These studies should also shed light on the relative importance of various antioxidant enzymes after selective oxidant stresses. Moreover, the development of synthetic scavengers of AOS and techniques for more effective targeting of cells of the lung will allow both preventive and therapeutic approaches to disease associated with exposure to environmental oxidants.

CONCLUSION

2 Anyhow all the four components have more or less similar docking energies and so all the four compounds can be used for good binding affinity in different pose site AEs activity. It might be expected that the active components isolated from *A. salvifolium* phytochemicals would have some pharmacological actions to promote the oxidative radical scavenging activity SOD, CAT and GPx enzymes. Further this may be confirmed by drug trials in in-vitro and in-vivo models to find out the optimum dose and its efficiency in binding actively AEs and reduce ROS related complications.

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