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Synthesis and *In-silico* Design of Gallic Acid Derivatives

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Abstract:- One of the most widespread phenolic acids in the plant world is gallic acid, also known as 3,4,5-trihydroxybenzoic acid. It is a crystalline substance that can be white or slightly yellow and finds extensive use in the food and pharmaceutical sectors. In the current study, three gallic acid compounds were created and then assessed for *in silico* investigations employing (PDB ID: 3VMP). When compared to common drugs like norfloxacin, it was shown that the three synthesised gallic acid derivatives with various aromatic aldehydes as schiff bases had a higher docking score and glide energy. In addition to their antioxidant properties, the newly created novel gallic acid derivatives have been shown in in silico studies to have significant potency against a variety of bacterial and fungal diseases, making them a crucial source for new antibacterial medications that focus on bacterial and fungal diseases in the future.

Keywords: *Gallic Acid; Schiff Base; Aromatic Aldehyde; 3VMP; Docking Score; Glide Energy.*

I. INTRODUCTION

Natural medicine molecules are documented in the about 5,000-year-old Indian Ayurveda system. The use of herbal medicine dates back 2500 years in Chinese literature [1,2]. Novel natural products have opened up opportunities for innovation in medication development and discovery during the past 20 years and have become crucial to the pharmaceutical and other industries [3,4]. Epidemiological data show that eating a diet high in plant-based foods greatly lowers the chance of developing many cancers and cardiovascular disorders, which raises the possibility that some dietary antioxidants could be useful tools for reducing cancer incidence and mortality [5]. The primary agents thought to be responsible for biological processes and illness healing are polyphenols, which are present in these therapies [6]. The most prevalent secondary metabolites in plants are phenolics, which are made primarily through the shikimate pathway from L-phenylalanine and L-tyrosine and contain one or more hydroxyl groups attached directly to aromatic rings. These compounds include simple phenols, phenolic acids, flavonoids, coumarins, stilbenes, hydrolyzable and condensed tannins, lignans, and lignins [7,8]. In general, phenolic compounds with one carboxylic acid group are referred to as "phenolic acids." One of the main types of phenolic compounds found in plants are phenolic or phenolcarboxylic acids, which are a form of phytochemical referred to as a polyphenol. They can be found in a wide range of plant-based meals, with the largest concentrations being in seeds, fruit and vegetable skins, and leafy greens. Rarely do they exist in free form; often, they are found in bound forms as amides, esters, or glycosides [9]. Hydroxybenzoic acid and hydroxycinnamic acid are the two primary sub-groups of phenolic acids [10]. In vitro antioxidant activity of phenolic acids is significantly higher than that of well-known antioxidant vitamins [11]. One of the most prevalent phenolic acids in the plant world is gallic acid, also known as 3,4,5-trihydroxybenzoic acid. It is a crystalline substance that can be white or slightly yellow and finds extensive use in the food and pharmaceutical sectors. Through a variety of chromatographic techniques, gallic acid has been isolated from various plant species, including Quercus spp. and Punica spp. However, from an industrial standpoint, gallic acid is produced through the hydrolytic breakdown of tannic acid using a glycoprotein esterase, namely tannase (12). Due to their ability to scavenge free radicals and act as antioxidants, gallic acid and its derivatives, including lauryl gallate, propyl gallate, octyl gallate, tetradecyl gallate, and hexadecyl gallate, can prevent the oxidation and rancidity of oils and fats. Consequently, they can be helpful as food additives. There are numerous scientific reports on the biological and pharmacological activities of these phytochemicals, with an emphasis on antioxidant, antimicrobial, anti-inflammatory, anticancer, cardioprotective, gastroprotective, and neuroprotective effects. Gallic acid and its ester derivatives are also used as flavourings and preservatives in the food industry (13).

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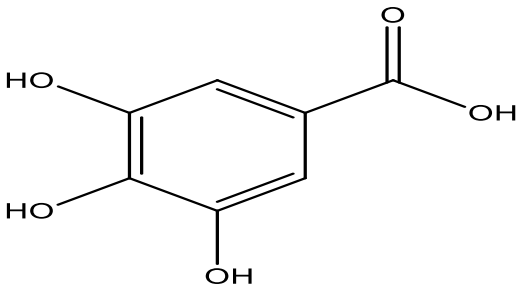

Fig 1 Chemical Structure of Gallic Acid

Table 1 Chemistry of Gallic Acid

S. No	Physiochemical property	
1.	Molecular formula	$C_7H_6O_5$
2.	Molecular weight	170.12 g/mol
3.	Solubility	Soluble in ethanol
4.	Appearance	White, Yellow
5.	Melting point	260^0C
6.	Density	$1.7g/cm^3$

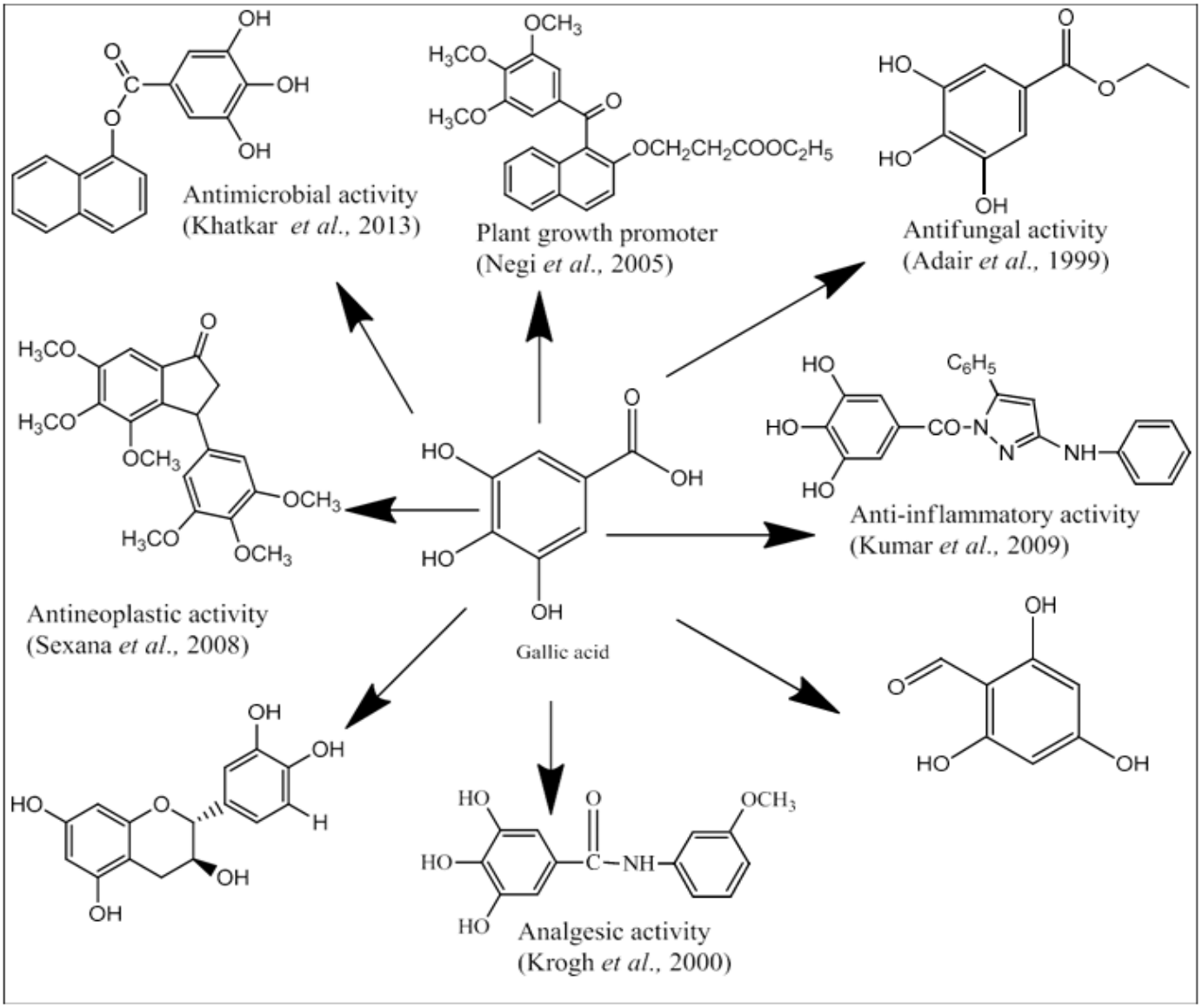

Fig 2 Reported Pharmacological Activities of Gallic Acid Derivatives

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II. MATERIAL AND METHODS

➢ *Synthetic Procedure*

Every analytical-grade reagent and solvent used in the investigation was purchased locally. Thin layer chromatography (TLC) was used to monitor the reaction's progress. Products were refined through recrystallization, and the purity of the compounds was assessed using TLC on a glass plate coated with silEvery solvent and analytical-grade reagent utilised in the experiment were bought locally. The reaction was followed using thin layer chromatography (TLC). Re-crystallization was used to purify the products, and TLC was used to determine the purity of the compounds on a glass plate covered with silica gel. IR spectra were captured using the spectrophotometer OPUS and G. Brucker software version 8.5.ica gel G. Brucker software 8.5 was used to record IR spectra: spectrophotometer OPUS.

- *Step 1:* In order to create gallic acid ester, the reaction mixture was concentrated, and the solid that had been separated was filtered, washed with water, and recrystallized from ethanol.
- *Step 2:* The first-stage ester was dissolved in 10 millilitres of ethanol with 1 millimole of hydrazine hydrate, and the mixture was then refluxed for six hours. The reaction mixture was evaporated, the TLC results of the reaction were obtained, the solid was washed with water, and then ethanol was used to recrystallize the reaction product.
- *Step 3:* An equimolar combination of hydrazides and aromatic aldehydes was refluxed with ethanol for four hours while being aided by concentrated sulfuric acid as a catalyst. The mixture of diethylether and ethylacetate was allowed to cool once the TLC-verified reaction was complete, and the solid that had split off was filtered, dried, and recrystallized.

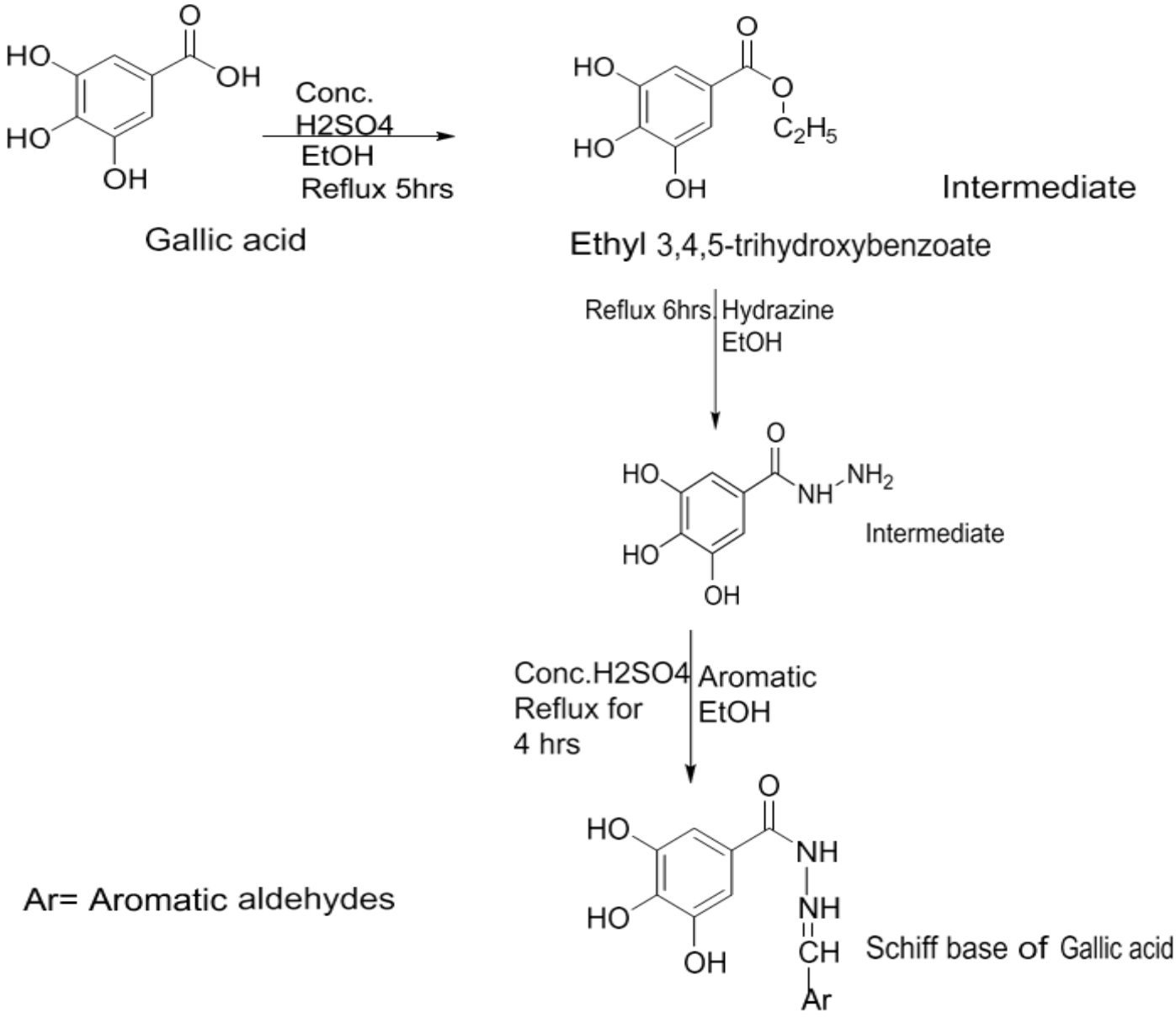


Fig 3 Synthesis f Novel Gallic Acid Nucleus Containing Derivatives by using (Scheme 1)

Table 2 List of Benzaldehydes used in Synthesis of Gallic Acid Derivatives

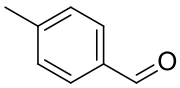
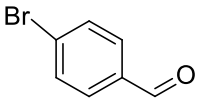
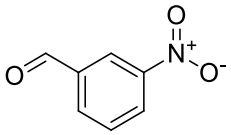
S.NO.	COMPOUND NAME	R1	IUPAC NAME OF THE AROMATIC BENZALDEHYDES
1.	GA1		4-Methylbenzaldehyde
2.	GA2		4-Bromobenzaldehyde
3.	GA3		3-Nitrobenzaldehyde

Table 3 Physicochemical Properties of the Synthesized Compounds (GA1- GA3)

Comp.	Molecular Formula	Colour	Molecular Weight(gm)	R*f* Value*	Yield (%)
GA1	$C_{16}H_{15}NO_4$	Brick red	285.29	0.65	68%
GA2	$C_{15}H_{12}BrNO_4$	Cream color	351.16	0.64	71%
GA3	$C_{15}H_{12}N_2O_6$	Light orange	317.26	0.72	63%

➢ *Molecular docking*

By simulating the interaction between a tiny molecule and a protein at the atomic level, the molecular docking method enables us to characterize how small molecules behave at the binding site of target proteins and to better understand fundamental biological processes [14]. The completion of the human genome project has opened up a growing number of novel therapeutic targets for drug development. The study of a number of structural characteristics of proteins and protein-ligand complexes has also been aided by the advent of nuclear magnetic resonance spectroscopy, crystallography, and high-throughput protein purification techniques. Due to these advancements, computational approaches can now be applied across the entire drug discovery process [15,16,17,18,19]. The two primary steps in the docking procedure are prediction of the ligand structure, as well as its positioning and orientation within these sites (often referred to as pose), and assessment of the binding affinity. The sample methods and scoring frameworks that will be discussed in the theory section are impacted by these two actions. Knowing the location of the binding site before doing any docking operations considerably increases the efficiency of those processes. The binding site is typically known before ligands are docked into it; by knowing the binding site's position before docking processes, efficiency is considerably increased. The binding site is typically known prior to docking ligands into it. One can also learn more about the sites by contrasting the target protein with a family of proteins that carry out a similar function or with proteins that have been co-crystallized with various ligands. Further information about the sites can be obtained by comparing the target protein to a family of proteins that share a similar function or to proteins that have been co-crystallized with various ligands. Software or internet services like GRID [20,21], POCKET [22], Surf Net [23,24], PASS [25], and MMC [26] that detect cavities without knowing the binding locations.

- *Examples of the Application of Molecular Docking to the Discovery of New Drugs*

Molecular docking has been the approach that has been utilised most frequently. There have been some remarkable accomplishments in this field, despite the fact that its principal application is in structure-based virtual screening to discover novel compounds that are active against a particular target protein [27]. Molecular docking has been the approach that has been utilised most frequently. There have been some remarkable accomplishments in this field, despite the fact that its principal application is in structure-based virtual screening to discover novel compounds that are active against a particular target protein [28].

- *Docking Investigations with Maestro 12.8*

Molecular docking has been the approach that has been utilised most frequently. There have been some remarkable accomplishments in this field, despite the fact that its principal application is n structure-based virtual screening to discover novel compounds that are active against a particular target protein. It is actually part of a workflow that includes numerous *in-silico* and experimental approaches and is not a stand-alone procedure [29].

- *Expected TPP and 1 Ligand Preparation for Docking*

The Maestro 12.8 software has tools for both protein and ligand optimization, such as assigning atomic charges to proteins to make them more polar, modifying ligands by assigning charge and rotatable bonds, figuring out the energy contribution of de-solvation during ligand-binding on proteins, and assigning grid maps on protein surfaces prior to ligand interaction by auto grid. Through the use of a new scoring method, efficient optimization, and multithreading, the aforementioned capabilities improve the speed, accuracy, and docking of molecular docking [30].

- *In a Simulated TPP, Protein Docking with L1 Metal Ion Molecules Serves as the Ligand*

In the current study, we calculated the binding-free energy, also known as docking score, which indicates the binding affinity of three ligands made of gallic acid derivatives and one prescription drug (Standard Pharmaceuticals: norfloxacin), to model TPP. According to the aforementioned docking study, the derivatives of gallic acid showed higher binding affinities and docking scores (-7.502, -8.459, and -9.434) than Norfloxacin, which had values of -4.614 and -4.614, respectively. For further research, the ligands with the model TPP's highest affinities are presented in Table 1 [31]. The Auto Dock Vina was replaced in the study by the drug discovery tool Glide energy (Maestro 12.8) of the Schrodinger programme. When docking calcineurin with inhibitors, Maestro 12.8 predicts binding affinity energies between (-9.434 kcal/mole to-4.614 kcal/mole), which is remarkably identical to the findings of the present investigation [32].

➢ *Gallic Acid Derivatives and Standard Drug Chemical Structure Composition*

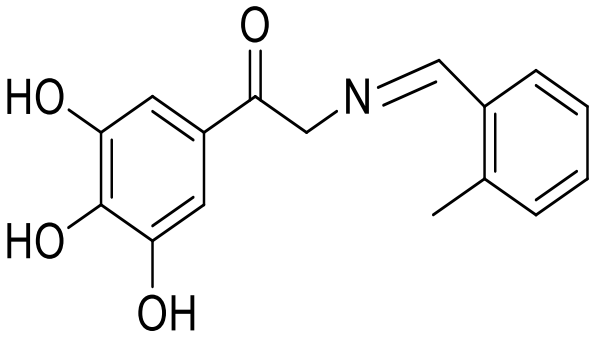


Fig 4 (Z)-2-((2-methylbenzylidene) amino)-1-(3,4,5-trihydroxyphenyl)ethanone

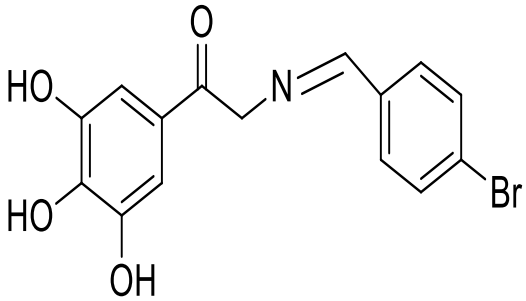


Fig 5 (Z)-2-((4-bromobenzylidene) amino)-1-(3,4,5-trihydroxyphenyl)ethanone

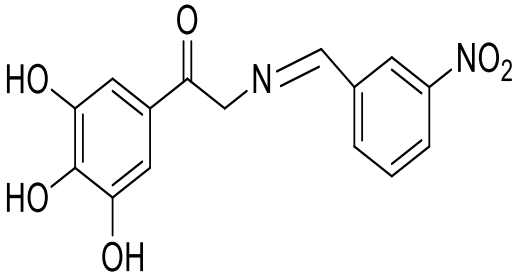


Fig 6 (Z)-2-((3-nitrobenzylidene) amino)-1-(3,4,5-trihydroxyphenyl)ethanone

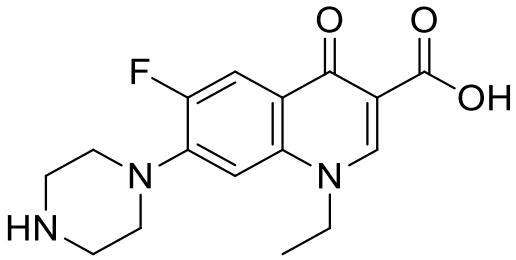
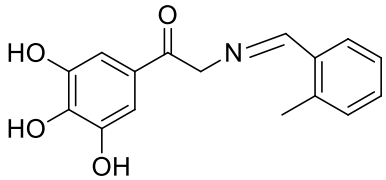
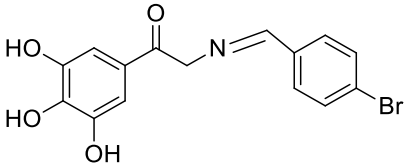
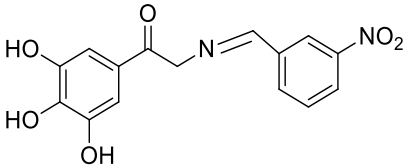
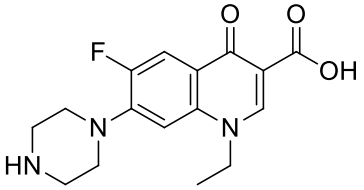


Fig 7 Chemical structure of norfloxacin

III. RESULTS AND DISCUSSION

Table 4 Three Gallic Acid Derivatives were Screened for In-Silico Screening against Standard Prescription Drug

S.No	Name of Compounds	Chemical Structure	Docking score (PDB ID: 3VMP)	Glide energy	Molecular Weight
1.	**(Z)-2-((2-methylbenzylidene)amino)-1-(3,4,5trihydroxyphenyl)ethanone**		-7.502	-38.790	285.29
2.	**(Z)-2-((4-bromobenzylidene) amino)-1-(3,4,5-trihydroxyphenyl)ethanone**		-8.459	- 40.430	350.16
3.	**(Z)-2-((3-nitrobenzylidene) amino)-1-(3,4,5-trihydroxyphenyl)ethanone**		-9.434	- 45.957	316.27

4.	**Norfloxacin (Standard drug)**		-4.614	- 40.675	355.79

➢ *PDB ID 3VMP:*
Crystal structure of dextranase from Streptococcus mutans in complex with 4,5-epoxypentyl alpha-D-glucopyranoside [33].

- *Classification:* HYDROLASE
- *Organism(s):* Streptococcus mutans
- *Expression System:* Escherichia coli
- *Mutation(s):* No

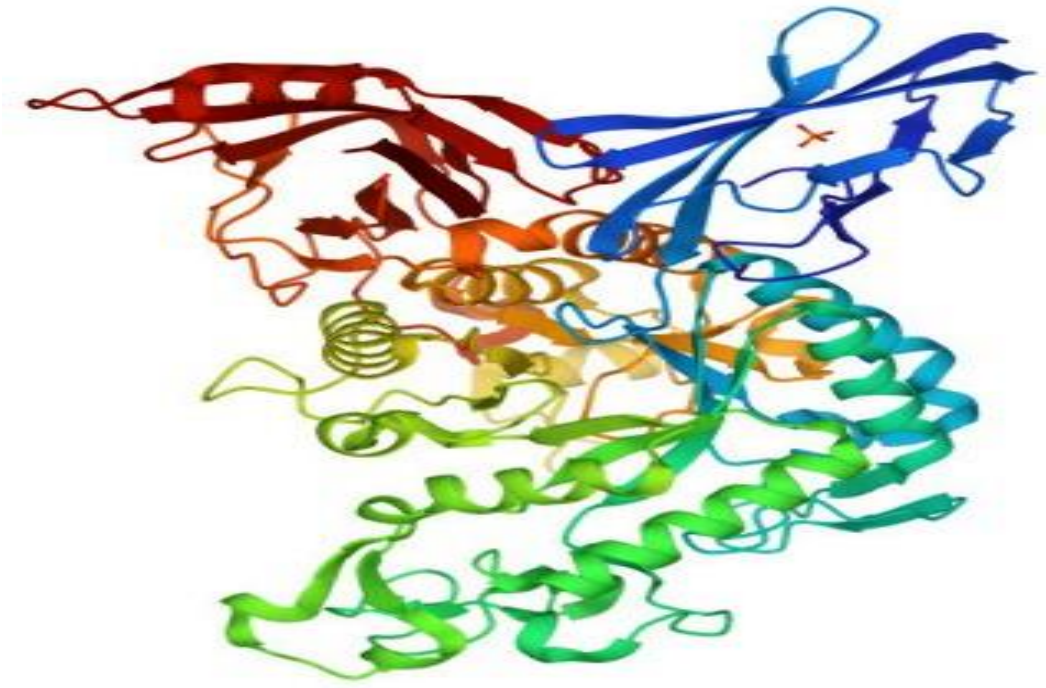


Fig 8 3D- Structure of Protein (3VMP)

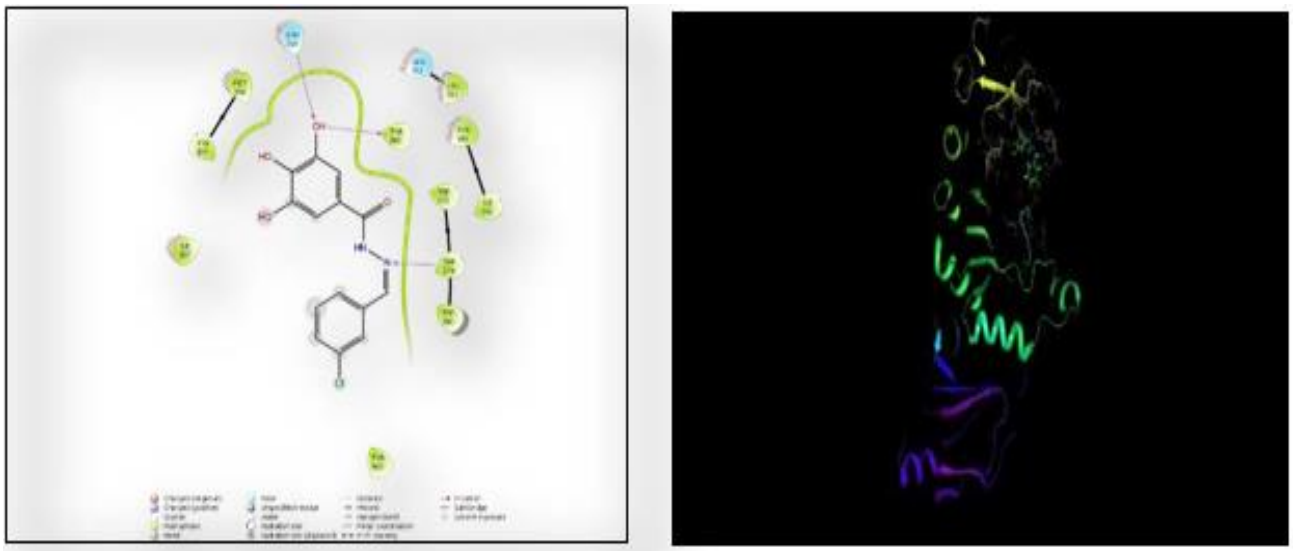


Fig 9 2D and 3D Diagrams of Docked Conformation Compound 1 Interacting with Amino Acid Residues

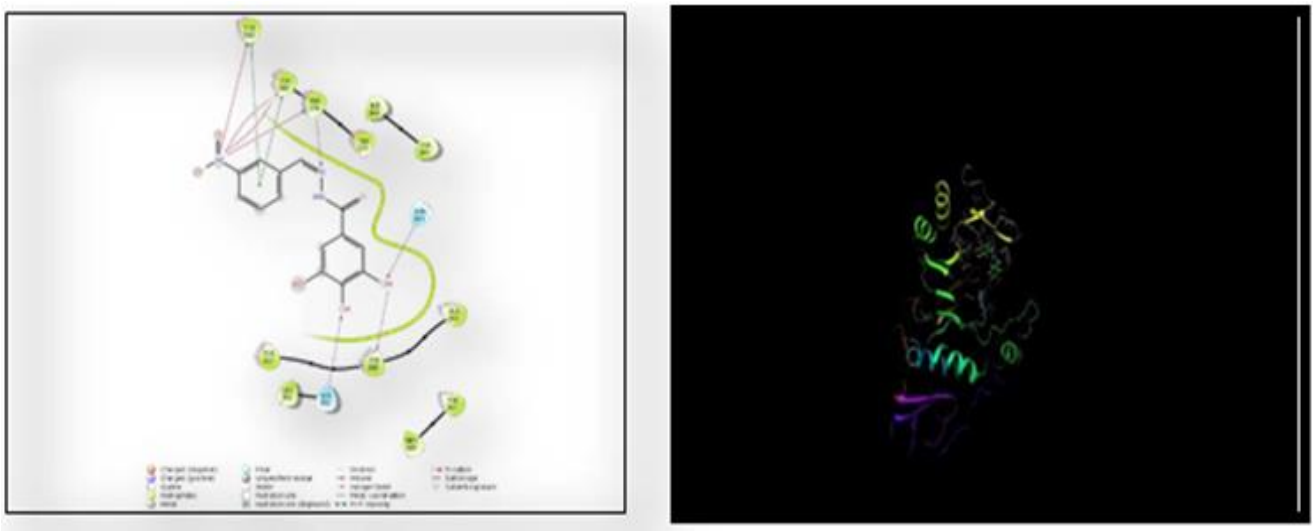


Fig 10 2D and 3D Diagrams of Docked Conformation Compound 2 Interacting with Amino Acidresidues

Fig 11 2D and 3D Diagrams of Docked Conformation Compound 3 Interacting with Amino Acid Residues

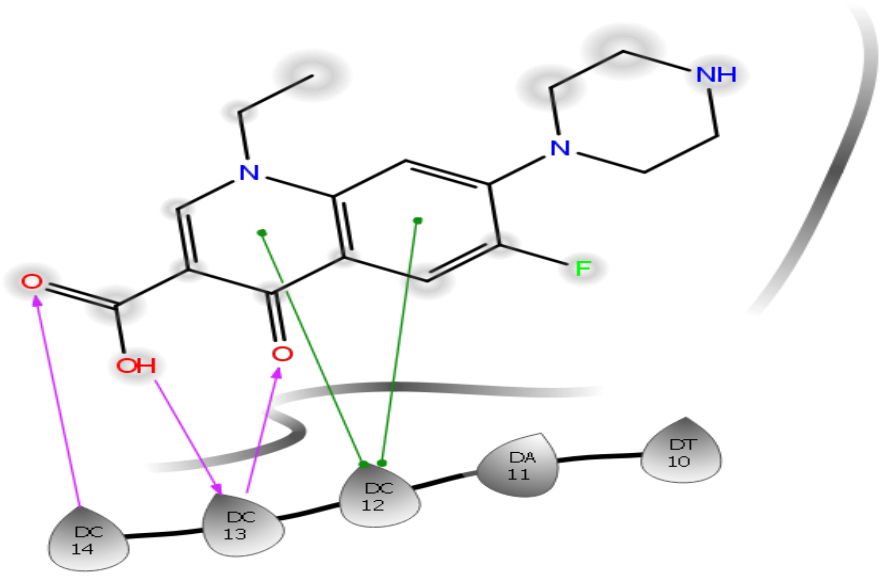


Fig 12 Norfloxacin 2D Diagrams of Docked Conformation Compound

IV. CONCLUSION

Although the foundation of our investigation is computational molecular docking, it is crucial that the scientific tool Maestro 12.8 employed for molecular docking research proves its validity. According to our research, the drug is capable of fighting off a number of bacterial and fungal infections with strength and effectiveness. It is founded on the creation and assessment of the three gallic acid derivatives in a computer simulation. Since the recently synthesised gallic acid derivatives have been shown in in silico studies to have significant potency against a number of bacterial and fungal diseases in addition to their significant antioxidant activity, they will be a key source for new antibacterial medications that target bacterial and fungal diseases in the future.

ACKNOWLEDGMENTS & DISCLOSURE OF CONFLICT OF INTEREST

The authors thank the reviewers for their insightful suggestions and declare there is no conflict of interest in this study.

❖ *Statement of Informed Consent*

Informed consent was obtained from all individual participants included in the study.

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