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# Screening of Bioactive Compounds and Potential Drug Targets for Cirrhosis Associated Cardiac Hypertrophy

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**ABSTRACT**

**Background and Objective:** Cardiovascular diseases (CVDs) are the leading cause of mortality worldwide, claiming the lives of an estimated 17.9 million people per year. Synthetic medicines are prone to toxicity and long-term side effects. Herbal medicine, on the other hand, is typically directed towards assisting the body's natural healing process and can decrease toxicity and increase therapeutic benefits. The objective of study is to quantitatively analyze the bioactive compounds of *Solanum album* and *Solanum nigrum* and *in silico* analysis to identify the protection pathway of cardiac tissues against cirrhosis-related cardiac hypertrophy using selected herbal compounds. **Materials and Methods:** Crude extracts were prepared with methanol, ethanol, hexane and chloroform solvents by extraction technique (Maceration method). Phytochemical analysis was carried out with a confirmatory test through TLC for terpenoids, alkaloids, flavonoids, phenols and tannins. Plant extracts of *Solanum album* and *Solanum nigrum* are characterized by UV-Vis Spectrophotometer (UV) and Fourier-Transform Infrared Spectroscopy (FTIR). *In silico* molecular docking with RCSB Protein Data Bank is used to get the three-dimensional structures of AGTR1 (PDB101) and PLC (PDB101). Ligand selection is done with the help of Pub Chem Target and ligand optimization is done by Drug Discovery Studio version 21.1.0 software and PYMOL 4.6.0 used for molecular docking analysis. **Results:** *In vitro* studies revealed that methanolic and ethanolic extracts of *Solanum nigrum* and *Solanum album* are rich sources of active secondary metabolites. Percentage inhibition against standard (ascorbic acid) showed that herbal extracts have excellent radical scavenging activity. The FTIR spectra of *Solanum nigrum* and *Solanum album* extracts showed peaks at 3323 and 3685 $cm^{-1}$ due to stretching of OH group. The $IC_{50}$ value of 81.746 µg/mL for *Solanum nigrum* and 74.048 µg/mL for *Solanum album* is reported. *In silico* studies highlights that Quercetin has binding energies of -8.4 kcal/mol compared to Angiotensin II (-7.5 kcal/mol) and Phosphatidylinositol 4,5 bisphosphate (-7.3 kcal/mol) with strong molecular binding action mechanism as compared to the conventional drugs. **Conclusion:** The plant extracts and their components have shown excellent antioxidant activities, *in silico* results of the study need *in vivo* pharmacological experiments for further verification to significantly improve the efficiency of compounds under study.

**KEYWORDS**

Cardiovascular disease, cirrhotic cardiomyopathy, angiotensin II, natural antioxidants, molecular docking, drug targets



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## INTRODUCTION

Despite accounting for a quarter of the world's population, South Asia already bears 60% of the worldwide burden of heart disease[1]. Cardiovascular disease (CVD) is a major cause of global death and morbidity. South Asians have a disproportionately high prevalence of coronary artery disease (CAD)[2]. Cirrhotic cardiomyopathy is a kind of cardiac dysfunction that comprises lower cardiac contractility with systolic and diastolic failure, as well as the presence of electrophysiological abnormalities, specifically QT prolongation[3]. Angiotensin (Ang II) exposure to the heart causes pathological and physiological cardiac hypertrophy, respectively, the signal transduction mechanisms for these effects are complex in nature. It is now clear that the activation of Ang type 1 receptors (AT1R) mediates the hypertrophic response. Reduced AT2R and Mas receptor expression and mitochondrial NADPH oxidase 4 activation may cause cardiac hypertrophy[4].

A clinical condition known as cirrhotic cardiomyopathy affects people with liver cirrhosis and is characterized by an aberrant and muted response to physiological, pathological or pharmacological stress, but is normal during rest due to increased cardiac output and tactility. Up to 50% of cirrhotic patients receiving liver transplants have symptoms of cardiac dysfunction and overt heart failure accounts for 7 to 21% of mortality following orthotropic liver transplantation[5]. Hypertrophy is brought on by either a protracted increase in the mean contractile "stress" (or tension) or, more likely, a sustained rise in the stroke energy expenditure per unit mass of heart muscle[6]. The development of this condition appears to be influenced by cardiac-adrenergic receptor dysfunction and its signaling role[7].

Herbal formulas are used as supplemental or alternative treatments since they are inexpensive, safe and have no negative side effects. The two most common conditions of dyslipidemia or increased lipids in the blood, are coronary heart disease (CHD) and cardiovascular disease (CVD), which cause atherosclerosis and cardiac arrest[8]. A well-known *in silico* structure-based method adopted extensively in drug development is molecular docking. Without knowing in advance the chemical makeup of other target modulators, docking enables the discovery of new medicinal compounds, the molecular prediction of ligand-target interactions or the delineation of structure-activity correlations (SAR)[9]. The desire to utilize herbal supplements is fueled by several factors the most important of which are their cost-effective therapeutic potential and safety when compared to mainstream contemporary medicines.

The current study attempted to highlight the potential of herbal extracts as possible treatments for Cirrhosis associated cardiac hypertrophy. Through various analyses and predictions, the indicated plant extracts and their components demonstrated antioxidant and inhibitory activities against standards. Based on the results of the *in silico* analysis, Quercetin improves the molecular mechanism of action against conventional drugs (Angiotensin II). The compound employed in this study may be useful in better-designed research and future therapeutic trials in animal models, obstructing pathogenicity's actions.

## MATERIALS AND METHODS

**Study area:** Medicinal plants named *S. album* and *S. nigrum*, were collected from local pansar. The authentication of plant samples was confirmed by the Taxonomist and Herbarium of the National Agricultural Council, Islamabad Pakistan.

**Research protocol:** Plants were dried under WHO guidelines. Plants were washed and dried under shade for two weeks. The flowers of plants were separated and pulverized in an electric grinder (NIMA Electric Grinder NM-83000). As 10 g of fine flower powdered will be extracted with 100 mL methanol and ethanol, in a conical flask at 37°C for 72 hrs utilizing electrical orbital shaker (VELP Scientifica Srl via Stazione,1620865 Usmate (MB)-Italy) then filtered through muslin cloth and. The filtrate is then dried on

a rotary evaporator Rocker Scientific Co. Ltd., 11F., No. 402, Sec. 1, Ren'ai Rd., Linkou Dist., New Taipei City 244014, Taiwan (R.O.C.) until all the solvents get evaporated and the only dry extract is left behind. The percentage yield of all the extracts was calculated by using formula[10]:

$$\text{Yield (\%)} = \frac{\text{Weight of dry extract}}{\text{Weight of dry plant}} \times 100$$

Plant extracts were screened for phytochemicals; 2 mg/mL of plant extract solution was prepared in respective plant solvent (methanol) and was screened for the following phytochemicals. Fourier-Transform Infrared (FTIR) spectroscopy is an effective tool for the chemical analysis of biological material. The mid-IR spectrum is the most widely used in the sample analysis, but the far- and near-IR spectrum also contributes to providing information about the samples analyzed. This study focused on the analysis of FTIR in the mid-IR spectrum. The ability of the extract to scavenge hydrogen peroxide ($H_2O_2$) was determined. Aliquot of 0.1 mL of extracts (25-400 µg/mL) was transferred into the Eppendorf tubes and their volume was made up to 0.4 mL with 50 mm phosphate buffer (pH 7.4) followed by the addition of 0.6 mL of $H_2O_2$ solution (2 mM). The reaction mixture was vortexed and after 10 min of reaction time, its absorbance was measured at 230 nm. Ascorbic acid was used as the positive control. The RCSB (The Research Collaboratory for Structural Bioinformatics Protein Data Bank) is used for accession of a target protein. Quercetin and alpha santalol chemical structures were collected from the PubChem substance database, while Angiotensin II and Phophatidylinositol 4,5 bisphosphate chemical structures were retrieved from the Chem spider database. The PYMOL tool was used to convert the MOL SDF format of these ligands to a PDB file. Drug Discovery Studio version 21.1.0 software is used to optimize the PDB coordinates of the target protein and the Quercetin molecule for docking research. Drug Discovery Studio version 21.1.0 and PYMOL 4.6.0 are used for analysis of target active binding sites. Finally, the Auto Dock Vina was used to dock protein and ligand based on an affinity.

## RESULTS

**Percentage yield:** Methanolic extract of *S. nigrum* gave a yield of 12.4% while ethanolic extract of *S. album* showed more yield of 18.3% as shown in Table 1 and 2.

**Phytochemical analysis:** Ethanolic plant extracts of *S. album* and methanolic plant extract of *S. nigrum* were tested for a total of five phytochemicals i.e. flavonoids, phenols, tannins and terpenoids were positive. All the results are summarized in Table 3.

**Thin layer chromatography:** The ethanolic extract of the *S. nigrum* plant successfully showed the presence of all tested secondary metabolites. Samples run in the methanol and acetic acid solvent system clearly showed the presence of phenols. The reddish-grey color appeared after the spray of $FeCl_3$, confirming the presence of phenols in *S. nigrum* plant extract with Rf values 0.68 and 0.65. Samples run

Table 1: Percentage yields of methanol and n-hexane of *Solanum nigrum*

| | Dry weight (g) | | Crude weight (g) | | (%) yield w/w | |
|---|---|---|---|---|---|---|
| Plant solvent | Methanol | n-hexane | Methanol | n-hexane | Methanol | n-hexane |
| *Solanum nigrum* | 10 | 10 | 1.24 | 0.34 | 12.4 | 3.4 |

Among two solvents the methanolic extract of *Solanum nigrum* showed high percentage yield

Table 2: Percentage yield of ethanol and n-hexane of *Solanum album*

| | Dry weight (g) | | Crude weight (g) | | (%) yield w/w | |
|---|---|---|---|---|---|---|
| Plant solvent | Ethanol | n-hexane | Ethanol | n-hexane | Ethanol | n-hexane |
| *Santalum album* | 10 | 10 | 1.83 | 0.34 | 18.3 | 3.4 |

Among two solvents the ethanolic extract of *Solanum album* showed a high percentage yield

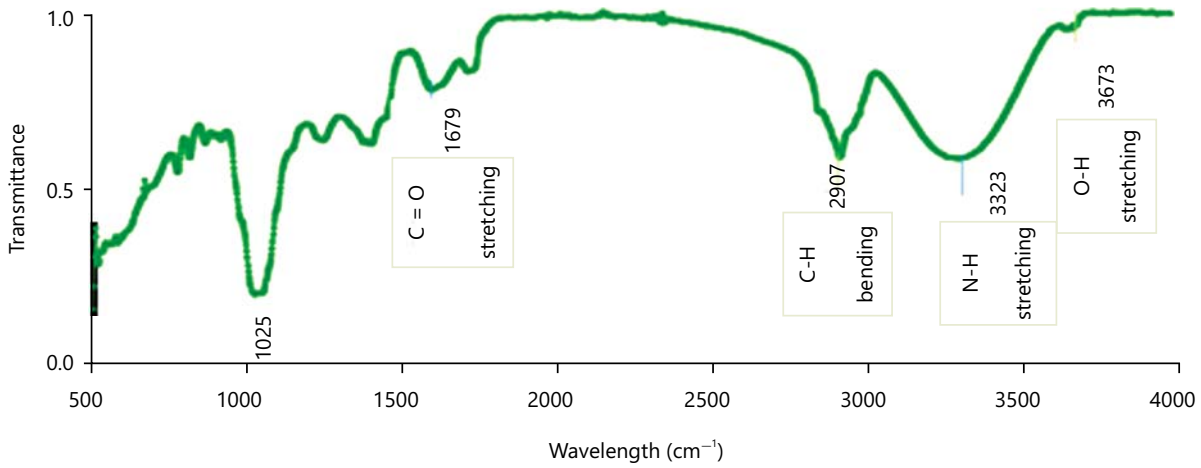


Fig. 1: FTIR spectrum of *Solanum nigrum* represents different peaks at various wavenumbers
There are five peaks in the spectrum region which depicts that plant extract contains complex compounds. Fingerprint region give reading at 1025 $cm^{-1}$ while other regions represent C-H bending, N-H stretching, C = O stretching and O-H stretching

Table 3: Rf values of various phytochemicals in methanolic berries extract of *Solanum nigrum* plant

| Phytochemicals | Solvent system | Rf value |
|---|---|---|
| Phenols | Methanol: Acetic acid | A = 0.68 |
| | | B = 0.65 |
| Alkaloids | Ethyl acetate: Chloroform | A = 0.58 |
| | | B = 0.59 |
| Flavonoids | Ethyl acetate: N-butanol: Water | A = 0.20 |
| | | B = 0.24 |
| Tannins | Chloroform: Methanol | A = 0.65 |

Among all the phytochemicals, solvent system methanol: Acetic acid showed best Rf value

in ethyl acetate and chloroform solvent system for alkaloids. The appearance of a creamy white color on the plate after Mayer's reagent spray confirmed the presence of alkaloids with the following Rf values 0.58 and 0.59 for the *Solanum nigrum* plant. Samples run in ethyl acetate, n-butanol and water solvent systems were tested for flavonoids. The appearance of a green color after the spray of 3% boric acid and 10% oxalic acid showed the presence of flavonoids with Rf values 0.2 and 0.24 for the *Solanum nigrum* plant. Samples run in chloroform and methanol were tested for tannins. The brownish-grey color appeared after the spray of $FeCl_3$,confirmed the presence of tannins in the extract with Rf values of 0.65 for *S. nigrum* plant extract. All the reults are shown in Table 3.

**FTIR analysis:** The FTIR spectra of *S. nigrum* plant extract give peaks at 1025, 1679, 2907, 3323 and 3673 $cm^{-1}$ summarize in Fig. 1. A peak at 3323 $cm^{-1}$ is due to the O-H group in the pyranose ring and the N-H group in prime. The FTIR absorption spectra of pure *S. nigrum* are shown in Fig. 1.

The FTIR absorption spectra of pure *S. album* are shown in Fig. 2. The FTIR spectra of *S. album* plant extract give peaks at 1027, 1398, 1611, 2916, 3323 and 3685 $cm^{-1}$. A peak at 1611 is due to the unsaturated ketone group. A peak at 2916 is due to the alkane group. A peak at 3323 $cm^{-1}$ is due to the O-H group in the pyranose ring and N-H group in prime and a peak at 3685 $cm^{-1}$ is due to the 0-H stretching alcohol group. All the results are shown in Fig. 2.

**Hydrogen peroxide radical scavenging activity:** The $IC_{50}$ value of methanolic fruit extracts of *S. nigrum* and standard ascorbic acid for scavenging of $H_2O_2$ was 81.746 and 89.462 µg/mL and the $IC_{50}$ value of

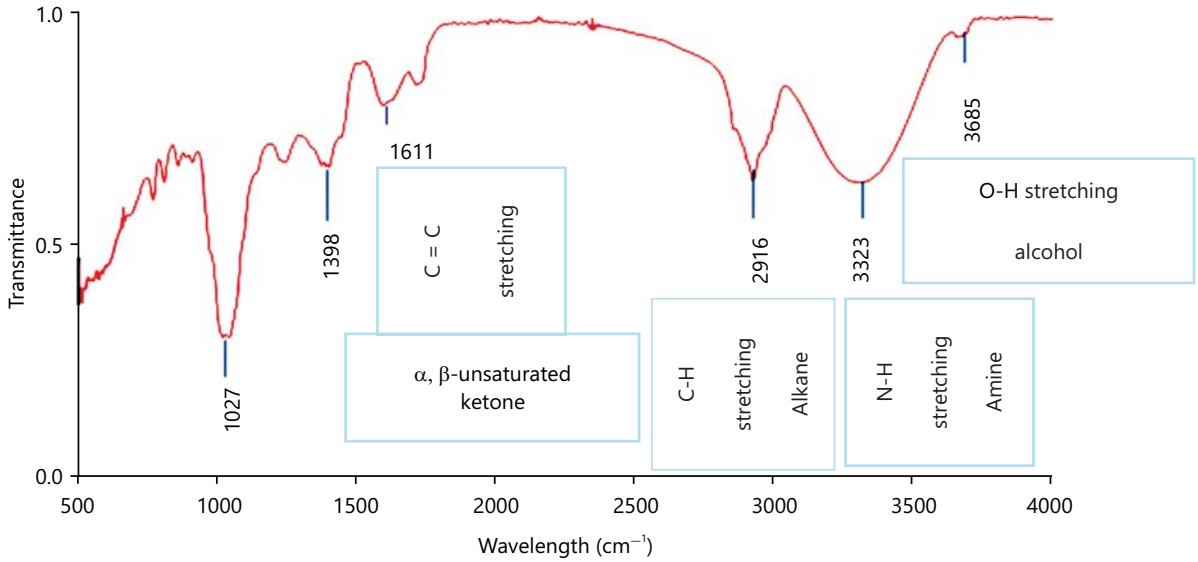


Fig. 2: FTIR spectrum of *Santalum album* represents different peaks at various wavenumbers

There are six peaks in the spectrum region which depicts that plant extract contains more complex compounds than *Solanum nigrum*. Fingerprint region give reading at 1027 and 1398 $cm^{-1}$ while other regions represent C = O bending, N-H stretching, C = O stretching and O-H stretching

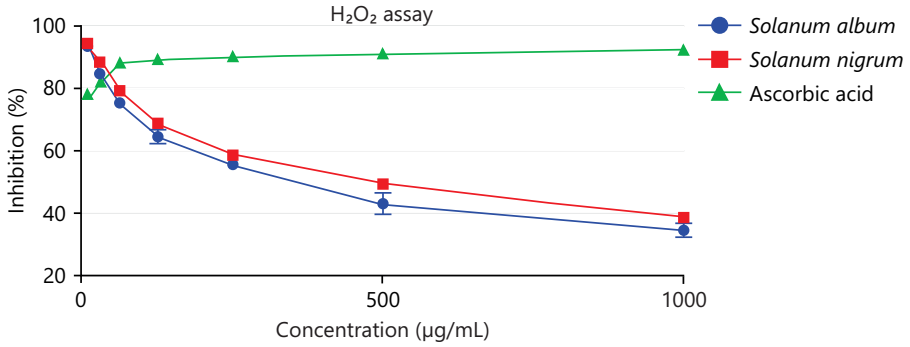


Fig. 3: Extract of *Solanum album* and *Solanum nigrum* at lowest concentration as compared to standard

This show maximum percentage inhibition as compared to standard (Ascorbic acid). These results justified the good insights for next animal model studies regarding dose concentration that should be less

ethanolic fruit extracts of *S. album* and standard Ascorbic acid for scavenging of $H_2O_2$ was 74.048 and 86.559 µg/mL as shown in the Fig. 3.

Ethanolic extract of *S. nigrum* shows $IC_{50}$ value of 81.74 µg/mL±1.8$^d$ while methanolic extract of *S. album* shows $IC_{50}$ value of 74.04 µg/mL±1.7$^d$ which justifies the good insight for antioxidant essays regarding less dose concentration for animal studies compared to ascorbic acid which shows the highest $IC_{50}$ value 86.59 µg/mL±1.9$^d$ and 89.462 µg/mL±1.6$^d$ that is not significant to scavange the free radicals.

***In silico* analysis:** Modes of confirmation from highest to lowest poses are shown in Table 4. By comparing the binding affinities among two ligands Quercetin from present study have the highest binding affinities -8.4 kcal/mol as compared to a natural substrate Angiotensin II having a binding affinity of -7.5 kcal/mol.

By comparing the binding affinities, Quercetin from present study has the highest binding affinities -8.4 kcal/mol and as compared to the natural substrate (Phosphatidylinositol 4,5 bisphosphate) having a binding affinity of -7.3 kcal/moL[11] shown in Table 5.

Table 4: Binding affinities of Quercetin and Angiotensin II at the active site of surviving

| Ligand | Ist | 2nd | 3rd | 4th | 5th | 6th | 7th | 8th | 9th |
|---|---|---|---|---|---|---|---|---|---|
| Angiotensin II | -7.5 | -7.0 | -6.8 | -6.6 | -6.5 | -6.4 | -6.3 | 6.3 | -5.90 |
| Quercetin | -8.4 | -8.3 | -7.9 | -7.9 | -7.7 | -7.5 | -7.4 | -7.4 | -7.30 |

Highest (9th) to lowest (1st) modes of conformation with corresponding RMS (root mean square) binding affinities in G (kcal/mol), [4]Modes of confirmation from highest to lowest poses

Table 5: Binding affinities of Quercetin and Phosphatidylinositol 4,5 bisphosphate at the active site of surviving

| Ligand | Ist | 2nd | 3rd | 4th | 5th | 6th | 7th | 8th | 9th |
|---|---|---|---|---|---|---|---|---|---|
| Phosphatidylinositol 4,5 bisphosphate | -7.3 | -7.2 | -6.9 | -6.8 | -5.9 | -5.7 | -5.6 | -5.5 | -5.4 |
| Quercetin | 8.4 | -8.3 | -7.9 | -7.9 | -7.7 | -7.5 | -7.4 | -7.4 | -7.3 |

Highest (9th) to lowest (1st) modes of conformation with corresponding RMS (root mean square) binding affinities in G (kcal/mol), [5]Highest to lowest modes of confirmation of Phosphatidylinositol 4,5 bisphosphate and Quercetin

## DISCUSSION

Ethanolic extract of *S. album* showed best yield of 18.3% as compared to methanolic extract of *S. nigrum* which is 12.4%. Similar results also supported the data that β-santalol and α- santalol were included in the ethanolic extract at the highest level with 19.6 and 16%[12]. The fractions that are obtained from phytochemical analysis revealed the best Rf value from methanol: Acetic acid solvent system in *S. nigrum* for screening of phenol while the Rf value of *S. album* is 0.2 in methanolic: Water solvent system. Data from literature greatly support the same Rf values for *S. nigrum* which showed two spots having Rf value of 0.65 and 0.68[13].

Phenols are screened as secondary metabolites for methanolic berries extract of *S. nigrum* plant. The amount of phenols that can be extracted depends on the solvent's polarity, indicating that high polarity solvents are ideal for extraction as reported in previous studies[14]. *Solanum nigrum* samples were screened with an FTIR spectrophotometer in the range of 500-4000 $cm^{-1}$ by solution casting method to determine the chemical interaction of each sample[15].

A functional group was found in similar tests, with absorbance peaks at 3,436, 2,919, 1,606, 1,386, 1,041 and 545 $cm^{-1}$ corresponding to -OH, -CH2, -COOH, C-C, C-C and C-H[16]. The FTIR absorption spectra of pure *S. album* was in the range of 500-4000 $cm^{-1}$ by solution casting method to determine the chemical interaction of each sample. Similar studies were reported regarding C = O stretching ,C-H stretching at 2916 [17]. The C-H methylation, also known as the "Magic Methyl Effect", has attracted a lot of attention recently due to its biological significance in medicinal chemistry[18]. Ethanolic fruit extracts of *S. nigrum* and methanolic extract of *S. album* showed the best $IC_{50}$ value of 81.74 and 74.04 µg/mL as compared to standard Ascorbic acid (86.59 and 89.462 µg/mL) for scavenging free radicals. Extracts were capable of scavenging hydrogen peroxide in a concentration-dependent manner[19]. Similar studies also supported the *S. nigrum* leaf extracts to scavenge free redicals[20]. *Solanum nigrum* at its lowest concentration shows maximum percentage inhibition as compared to standard Ascorbic acid[21].

By comparing the results it is assumed that Quercetin from present study have the highest binding affinity of -8.4 kcal/mol as compared to a natural substrate Phosphatidylinositol 4,5 bisphosphate and Angiotensin II having a binding affinity of -7.3 and -7.5 kcal/mol. According to *in silico* research, AT1R blockade has been demonstrated to inhibit the regression of Ang II-induced cardiac hypertrophy[22]. Kang *et al.*[23] reported that Quercetin binds with AT1R blockers, like losartan, to effectively reduce cardiac hypertrophy[23]. Though the precise causes of the shift from Ang II-induced physiological to pathological cardiac hypertrophy remain unclear, one of the most significant pathogenic elements thought to be involved in this process could be the establishment of a critical level of oxidative stress. To verify quercetin's effectiveness with ATIR blockers, more *in vivo* research could be conducted.

## CONCLUSION

The current study attempted to highlight the potential of herbal extracts as possible treatments for Cirrhosis associated cardiac hypertrophy. Through various analysis and *in silico* predictions, the indicated plant extracts and their components demonstrated antioxidant activities. Based on the results of the Insilico analysis, Quercetin may improve the molecular mechanism of action against conventional drugs targeting Angiotensin II which needs to be verified by *in vivo* study.

## SIGNIFICANCE STATEMENT

The quantitative and qualitative analysis of bioactive compounds revealed the therapeutic properties and presence of different types of important functional groups in *S. album* and *S. nigrum*. *In vitro* studies revealed that methanolic and ethanolic extracts of both plants yield active secondary metabolites with excellent radical scavenging activity. With the help of *in silico* analysis, unique protection pathways have been identified against cirrhosis-related cardiac hypertrophy using a selected herbal compound, quercetin which may improve the molecular mechanism of action against conventional drug target Angiotensin II. The compound employed in this study may be useful in better understanding of designing targeted drugs for future therapeutic trials in animal models.

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