https://doi.org/10.48048/tis.2023.4664

Screening *In silico* Antidepressant Activity of Aqueous Extract of Leaves of *Rumex acetosa L.*

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Received: 12 June 2022, Revised: 28 July 2022, Accepted: 4 August 2022, Published: 17 January 2023

Abstract

The main objective of this study is to obtain extracts of *Rumex acetosa* leaves using various solvents, characterize these extracts and finally evaluate *in silico* antidepressant activity. *Rumex acetosa* belongs to polygonaceae family and is often called sorrel. This plant's leaves were gathered and extracted using a variety of solvents including petroleum ether, ethyl acetate, ethanol, chloroform, and ultimately water. All these extracts are explored to check for various phytoconstituents by commonly used phytochemical screening methods. It was found that aqueous extract of *Rumex acetosa* (AERA) contained many phytoconstituents like alkaloids, flavonoids, glycosides, and anthocyanins. This aqueous extract was further screened by FTIR, HPLC, and GCMS analysis techniques. In FTIR analysis, aqueous extract of *Rumex acetosa* showed peaks at 1163.11and 1060.88 cm^{-1}corresponding to anthocyanins. HPLC analysis showed the presence of peaks with the retention time of 6.75, 18.94, 25.19, 28.04, 34.72 and 39.37 min corresponding to sennoside, aloe-emodin, rhein, emodin, chrysophanol, and physcion respectively. In GCMS analysis, peaks at 18.15, 18.50, 20.32, 20.48 and 24.99 correspond to rhein, dibutyl phthalate, emodin, octadecanoic acid, and chrysophanol respectively. Five phytoconstituents - aloe-emodin, chrysophanol, emodin, physcion, and rhein - are further assessed for *in silico* antidepressant effectiveness based on characterization data. As rhein has the highest negative value of glide energy, it indicates a stronger binding affinity for MAO-A than all other screened constituents. Thus, the study concludes regarding *in silico* anti-depressant activity against MAO-A. Further, present research puts forth a way to carry out the isolation of therapeutically proven phytoconstituents and to evaluate these constituents for their biological activity.

Keywords: Sorrel, FTIR, HPLC, GCMS, Docking study, Rhein, Physcion, Emodin

Introduction

Mood disorders have been the second major reason of disability in all ages, according to a WHO (World Health Organization) report. Depression is a common factor and it ends up incapacitating mental condition, places a significant health burden on society [1]. People with major depression show symptoms which reflect in alterations in brain monoamine neurotransmitters, particularly serotonin (5-HT) and norepinephrine (NE) [2]. Dopamine (DA) appears to be implicated in pathogenesis and in therapy of depression, according to clinical findings [3]. Tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), specific serotonin-norepinephrine reuptake inhibitors (SNRIs), 5-HT2 receptor antagonists, and other heterocyclics are among the drugs utilized in clinical practice [4].

Each medicine used to treat this disease has a 60 % success rate. Furthermore, most medications need many weeks of therapy before the signs and symptoms improve and antidepressants have significant negative effects [5].Thus, the great incidence of depression as well as the fact that a considerable number of people do not react well to any currently available antidepressants or therapies highlights the need for novel antidepressant medicines. A plethora of antidepressant drugs are currently accessible, apparently working through various pathways such as serotonergic, noradrenergic, andor dopaminergic systems [6]. These drugs, on the other hand, can cause drowsiness, apathy, tiredness, sleep disruption, cognitive impairment, and sexual dysfunction. As a result, there is still a pressing need for novel antidepressants that are both effective and well

tolerated. In the treatment of depression, herbal plants utilized in medicines can be considered as viable options and these have made great development in the last decade [7].

In our search for supplementary materials, we came upon *Rumex acetosa* L, a herbal plant with ethnomedicinal qualities. Plants were essentially present before human civilisation. *Rumex acetosa L.* species have received widespread acceptance since humans began using plants and herbs as remedies for illnesses and afflictions owing to their healing properties and different therapeutic effects [8]. *Rumex* is a member of the Polygonaceae family and is found all over the world. They are mostly found in the northern hemisphere, Europe, Asia, Africa, and North America [9]. The most widely used components in traditional medicine are the aerial parts, fresh plant juice, leaf, root, and seed. *Rumex acetosa* (sorrel) is a perennial plant. Sorrel or garden sorrel is the common name for this plant. It grows as a garden herb or as a leaf vegetable (pot herb) in grasslands. For decades, farming of common sorrel has been done. The species name, acetosa, is the Latin word for "vinegary" denoting the acidic flavour of the plant [10]. Its leaves have a flavour similar to kiwi fruit or sour wild strawberries and can be puréed to add in soups and sauces or added to salads. The plant's bitter flavour is caused by Oxalic acid [11,12].

Due to its astringent, spasmolytic, and antithrombotic qualities, *Rumex* species have been used in medicine for millennia [13,14]. The phytochemical components of *R. acetosa* extract include monomeric flavan-3-ols (catechin, epicatechin, and epicatechin-3-O-gallate), A and B type procyanidins, and propelargonidins (15 dimers, 7 trimers and 2 tetramers) [15,16]. The therapeutic benefits of this plant are connected to its tannin content and can be used to cure a variety of diseases. Previous research found *R. acetosa* to have antioxidant [9,17], antihypertensive, antiviral, and anticancer properties [18-20]. However, there was no information on the antidepressant properties of *R. acetosa* L. leaf aqueous extract. Therefore, this study was designed to extract and evaluate *in silico* antidepressant activity of leaves of *R. acetosa*.

Materials and methods

Materials

In December 2019, *Rumex acetosa* leaves were harvested in and around Hyderabad. Plant samples were authenticated at the Botanical Survey of India's Deccan area in Hyderabad. It was kept in the Pharmacognosy department under Specimen no. MESCO-PCOG-2020-016. SD Fine Chemicals Limited was preferred for procuring chemicals like chloroform, ethyl acetate, ethanol, and petroleum ether. The compounds utilised in the investigation are all of the Laboratory Reagent variety.

Methods

Extraction of R. acetosa leaves by using soxhlet apparatus

As previously stated, *R. acetosa* leaves were collected and authenticated. These leaves were examined for contaminants, dried, ground to a coarse powder, and then subjected to sequential solvent extraction using the Soxhlet system. The following technique was used for Soxhlet extraction: Defatting of plant material was performed using 500mLpetroleum ether at 55 °C, and obtained petroleum ether extract of *Rumex acetosa* (PERA), followed by extraction using various solvents such as chloroform500mLat 55 - 60 °C, and obtained chloroform extract of *Rumex acetosa* (CERA); ethyl acetate 500 mL at 55 - 65 °C, and obtained ethyl acetate extract of *Rumex acetosa* (EAERA); ethanol 500mLat 55 - 60 °C, and obtained ethanolic extract of *Rumex acetosa*(EERA); and water 500mLat 65 - 75 °C, and obtained aqueous extract of *Rumex acetosa* (AERA). After allowing the obtained extracts to air dry for a 140 h, a semisolid form was obtained. The following formula was used to compute the percent yield for all of the collected extracts;

%Yield = (Weight of extract obtained in grams/Total weight of raw material) ×100

Phytochemical analysis of R. acetosa leaves with different extracts

To identify the presence of alkaloids, cardiac glycosides, tannins, phytosterols, proteins, amino acids, and flavonoids, preliminary phytochemical analysis was performed using Khandelwal's standard methods [21,22]. The Fourier transform infrared (FTIR) spectrophotometer is the technique for detecting functional groups in substances. For the FTIR study, the dried aqueous extract was employed. A translucent sample disc was created by encasing 10 mg of dried extract powder in 100 mg of KBr pellet. Each plant specimen's

powdered sample was analysed using FTIR spectroscope (Shimadzu, Japan) with a scan range of 400 to 4,000 cm^{-1} and a resolution of 4 cm^{-1}.

HPLC (Shimadzu Japan) analysis using a C18 column was used to further evaluate the phytochemistry of *R. acetosa*. The flow rate was set to 1mL/min and the instrument was configured to run at room temperature. Two solvents comprise the mobile phase: 0.1 % trifluoroacetic acid in water (Sol-A) and 0.1 % trifluoroacetic acid in acetonitrile (Sol-B). For 24 h, 100 mg of extract was dissolved in 5 mL of methanol (5 °C). This extract solution was centrifuged at 2,500 rpm for 15 min before collecting the supernatants. It was filtered using a 0.45 micrometer membrane. This was then diluted with twice distilled water. A total of 100 µl of the filtrate was injected, and the analysis was performed at 521 nm. The elution programme for analysis is as follows: For the first 5 min, 5-15 % Sol-B was allowed, then for the next 10 min, 15-25 % Sol-B was allowed, then 25-100 % Sol-B for the next 15 min, and finally 100 % Sol-B for 30-40 min. Chlorogenic acid was used as an internal standard [23,24].

10 g of AERA was dissolved in 95 % ethanol for 5 h of GC-MS analysis. To eliminate sediments and traces of water from the filtrate, the extract was filtered using Whatmann filter paper No. 41 with 2 gm sodium sulphate. The sodium sulphate and filter paper were steeped in 95 % ethanol before filtering. Both polar and nonpolar phytocomponents of the plant material were present in the extract. GC-MS analysis on this sample was performed using the "Trace DSQ GC-MS" analyser. A fused silica capillary column with a 30 m length, 0.25 m thickness, and 0.25 mm diameter is employed in this setup. Helium gas was employed as a carrier at a constant flow rate of 1mL/min. The injection was 2 µl in volume. Temperatures of the injector and ion source were kept at 250 and 280 °C, respectively. By comparing each component's average peak area to the total areas, the relative percentage quantity of each component was calculated. The GC-MS study was performed at Osmania University's University College of Technology in Hyderabad's Central Instrumentation Research Laboratory.

In silico analysis of R. acetosa leaves aqueous extract

The antidepressant effects of AERA were investigated *in silico* using the computational structure of MAO-A retrieved from the Protein Databank website with PDB Id: 2z5y.Unconnected water molecules in multiples of one were deleted to enhance the structure. The energy of the overall structure was decreased using the OPLS-2005 force field and the protein preparation wizard tool from the Schrodinger suite. To fulfil the valences, hydrogen atoms are added. Following that, amino acids are added to stabilise the side chains. Using the Glide XP docking method, the structurally optimised protein was used to study protein-ligand interactions of the dataset ligands.

To begin, all of the dataset ligands were docked into a 3D grid that was created around the protein's binding site. The glide score, which is a mixture of hydrophilic, hydrophobic, metal-binding groups, Vander Waals energy, frozen rotatable bonds, and polar contacts with the receptor, was used to quantify binding interactions and efficiency [25].

Post molecular docking calculations were performed using the Schrodinger suite's Prime MM/GBSA (molecular mechanics-based generalised born/surface area) module to determine binding energies of docked complexes. This energy is made up of a combination of OPLS molecular mechanics energies (EMM), an SGB polar solvation model (GSGB), and a non-polar solvation term (GNP) that accounts for non-polar solvent accessible surface area and Vander Waals interactions. The results of molecular docking were rescored using an energy function that contained a detailed description of the binding contributions. The following equation is used to express the total free energy of binding;

$\Delta G_{bind} = G_{complex} - (G_{protein} + G_{ligand})$, where ΔG_{bind} is the ligand's binding energy.

Results and discussion

Extraction and phytochemical screening of *R. acetosa* leaves

The presence of a high number of physiologically active chemicals in several species of Rumex has made it important in medicine and the pharmaceutical sector [26]. *Rumex acetosa L*. is a wild perennial plant, well known for the presence of many biologically active phytoconstituents. All the parts of the plant including the leaves are important sources of various therapeutic constituents [9]. Soxhlet apparatus was used for successive solvent extraction of leaves of *R. acetosa*. Extracts obtained are black and semi-solid in

consistency. 11.1 % is the highest % yield with AERA. All these extracts are screened for the presence of different phytoconstituents. Alkaloids, phytosterol, and flavonoids were found in PERA. It is important to mention that AERA contains all the phytoconstituents viz., alkaloids, carbohydrates, glycosides, tannins, phytosterols, proteins, amino acids, flavonoids, and anthocyanins. The presence of anthraquinone derivatives in this plant is reported by Cos [27]. Many types of constituents including flavonoids are reported in aerial parts of Acetosa [28]. **Table 1** shows the presence of components in various extracts.

Table 1 Phytochemical analysis of various *R. acetosa* extracts.

SNO	Phytochemical constituents	PERA	CERA	EAERA	EERA	AERA
	Alkaloids					
1	1. Mayers test	+	+	+	+	+
	2. Wagners test	+	-	+	-	+
	Carbohydrates					
2	1. Molish test	+	+	+	+	+
	2. Benidicts test	-	+	+	+	+
	Cardiac glycosides	-	+	+	+	
3	1. Legals test	-	+	+	+	+
	2. Killerkallani test					+
4	Anthraquinone glycosides 1. Borntrager's test	-	+	+	+	+
	Tannins	-	+	+	+	+
5	1. Iodine test	-	-	+	+	+
	2. Gelatin test					
	Phytosterol	+	+	+	+	+
6	1. Salkowiskis test	-	+	-	+	+
	2. Libermannbuchard test					
	Proteins and aminoacids	-	+	-	+	+
7	1. Ninhydrin test	-	+	-	-	-
	2. Millons test					
	Flavonoids					
8	1. Alkaline reagent test	+	-	+	+	++
	2. Lead acetate test	-	-	+	+	++
9	Anthocyanins	-	-	-	-	++

FTIR, HPLC and GCMS analysis of AERA

In FTIR analysis, absorption peaks belonging to C=C, C-H aromatic ring and O-H bonds were found at 1,467 - 1,431 cm^{-1}, 3,049 and 3,162.71 cm^{-1} respectively in AERA. These correspond to -CH stretching, -OH carboxylate, C=C aromatic ring stretching, -CO tertiary alcohol stretching, -CO secondary alcohol stretching, -N-H bending vibration, and -C-H aromatic ring stretching, respectively (**Figure 1** and **Table 3**). Very similar peaks are shown with *R. acetosa* extract by Ahn [29].

HPLC analysis showed the presence of peaks with the retention time of 6.75, 18.94, 25.19, 28.04, 34.72 and 39.37 min corresponding to sennoside, aloe-emodin, rhein, emodin, chrysophanol, and physcion respectively.

Further, to identify the presence of different constituents GC-MS analysis was conducted. The retention time of 1.082 represents nitro acetonitrile with a % area of 4.80%. Pentaborane, bicycle (7.2.0) undec-4-ene, 4,11,11-trimethyl-8-methylene, Cycloheptasiloxane, tetradecamethyl, Phthalic acid, di-(1-hexen-5-yl) ester, and Benzoic acid, 4-formyl are the other peaks with retention times of 1.22, 2.45, 10.45, 12.36, 14.06 and 14.18 min. Whereas peaks at 18.15, 18.50, 20.32, 20.48 and 24.99 min, correspond to rhein, dibutyl phthalate, emodin, octadecanoic acid, and chrysophanol, respectively (**Figure 2** and **Table 2**). Phytoconstituents found in our study are reported for various activities in many other studies. It has been shown that emodin, a

significant anthraquinone component of *R. acetosa* extract, has the potential for P-gp mediated drug interaction and has a variety of pharmacological actions, including antidiabetic and anticancer activity [30-32].

Similarly, chrysophanol and another derivative of chrysophanol named chrysophanol-8-O-d-glucoside are reported in *R. acetosa* and both are found to be effective in P-gp inhibition. Chrysophanol was also reported for various biological activities like neuroprotective, anti-cancer, anti-viral and anti-inflammatory [33]. Our results are consistent with Wegiera [34], this group of scientists used Reverse Phase-HPLC to identify different derivatives of anthraquinone from methanolic extracts of *R. acetosa* roots, leaves, and fruits. These phytoconstituents include emodin, chrysophanol, physcion, aloe-emodin, rhein, barbaloin, palmatin, and sennosides A and B.

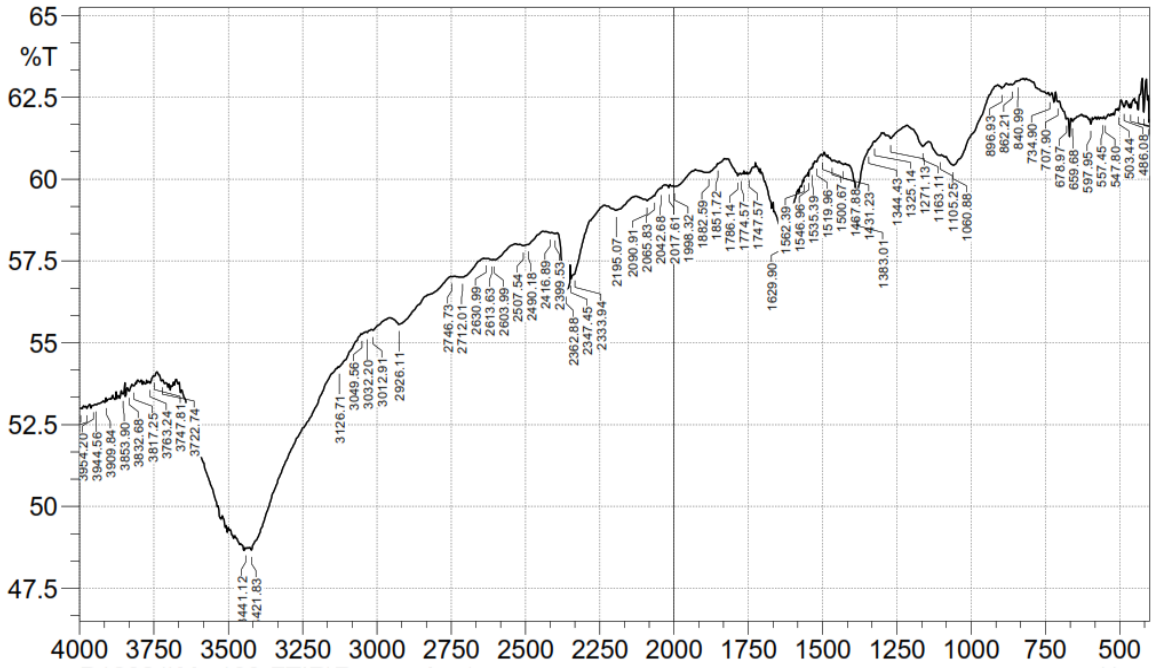

Figure 1 Presence of different functional groups is identified by FTIR analysis of AERA. (X axis- wave number in cm^{-1}; Y axis- Transmittance in %)

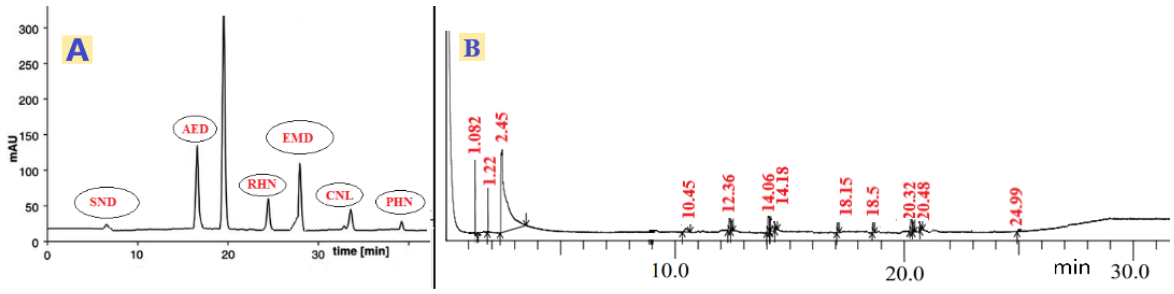

Figure 2 A- HPLC analysis of AERA, B- GCMS analysis of AERA.

Table 2 Identification of different constituents by GC-MS analysis of AERA.

R. TIME	Name	Molecular formula	Molecularweight (g/mol)	Area %	Base m/z value
1.082	Nitro acetonitrile	$C_2H_2N_2O_2$	86.05	4.80	5.60
2.45	Pentaborane	$C_{14}H_{14}NO_4PS$	323.31	42.14	81.80
10.45	Bicyclo (7.2.0) undec-4-ene, 4,11, 11-trimethyl-8-methylene	$C_{15}H_{24}$	204.35	1.04	41.05
12.36	Cycloheptasiloxane, tetradecamethyl-	$C_{14}H_{42}O_7Si_7$	519.07	2.69	73.90
14.06	Phthalic acid, di-(1-hexen-5-yl) ester	$C_{20}H_{26}O_4$	330.4	2.35	148.95
14.18	Benzoic acid, 4-formyl-	$C_8H_6O_3$	150.13	5.49	49.7
18.15	Rhein	$C_{15}H_8O_6$	284.22	1.08	4.05
18.5	Dibutyl phthalate	$C_{16}H_{22}O_4$	278.34	2.11	148.9
20.32	Emodin	$C_{15}H_{10}O_5$	270	11.50	69.10
20.48	Octadecanoic acid	$C_{18}H_{36}O_2$	284.4	4.87	3.05
24.99	Chrysophanol	$C_{15}H_{10}O_4$	254.24	0.14	73.00

Table 3 Frequency range of different absorption peak in FT-IR.

Absorption peak	Frequency range cm^{-1}
O-H stretching	3,162.71
CH stretching	2,926.11
CO stretching	1,629.90
C=C stretching of aromatic ring	1,467-1,431
CO stretching of tertiary alcohol	1,163.11
CO stretching of secondary alcohol	1,060.88
C-H stretching for aromatic ring	3,049
-N-H bending vibration	3,441.12 - 3,421.83

The most often used computer approach for exploring the interactions between organic compounds and biological macromolecules is molecular docking [35]. Five phytoconstituents, including aloe-emodin, chrysophanol, emodin, physcion, and rhein, are further assessed for *in silico* antidepressant effectiveness based on characterisation data. This was accomplished by employing MAO-A, 2z5y as a target protein. The flavin adenine dinucleotide-dependent enzyme is monoamine oxidase (EC 1.4.3.4). This is mostly found on the mitochondrial outer membrane. The principal function of this enzyme is monoamine oxidative deamination [36]. MAO-A and MAO-B are 2 isoforms of MAO with distinct inhibitor sensitivity, amino acid sequences, tissue distribution and substrate preference [37]. Noradrenaline and serotonin (5-hydroxytryptamine) are preferentially deaminated by MAO-A, whereas -phenyl-ethylamine and benzylamine are preferentially deaminated by MAO-B [38]. Individuals with depression have higher MAO-A concentrations in different brain areas (such as the prefrontal cortex, hippocampus, and midbrain), even after they have recovered. However, MAO-A densities found in the anterior cingulate cortex are linked to the recurrence of depressive symptoms [39].

The molecular docking score function can predict crystallographic binding orientations. Glide Score is the scoring function used that approximates the ligand binding free energy based on empirical data. Ligand binding is known to be affected by electrostatic and vander Waals interactions. Docking accuracy, database enrichment, and binding affinity prediction are optimized by it. Because it replicates binding free energy, more negative numbers suggest tighter binders [40]. Glide XP builds many protein ligand complexes for each protein ligand interaction, but only the complex with the greatest EModel energy is included in the findings. Aloe-emodin shows binding interactions with GLY (443) and GLN (215) amino acid of MAO-A, 2z5y protein. Thus aloe-emodin shows 2 hydrogen bonds with the bond distance of 2.53 and 1.77 Å. Dock score, glide energy, and emodel energy was found to be −9.799, −28.57 and −49.107 respectively (**Figure 3**). Chrysophanol shows binding interactions with GLY (443) amino acid of MAO-A, 2z5y protein. As there is only one hydrogen bond with the distance of 2.51 Å, glide energy and emodel energy are −26.09, −41.98 respectively. This is slightly greater than the aloe-emodin (**Figure 4**). Emodin does not show binding interactions with amino acids of MAO-A, 2z5y protein (**Figure 5**).

Physcion shows binding interactions with ASN (181) amino acid of MAO-A, 2z5y protein. Dock score of physcion was found to be −8.48, whereas glide and emodel energy were found to be −22.248, −38.407 respectively **(Figure 6)**. Rhein shows binding interactions with MET (445), and TYR (69) amino acid of MAO-A, 2z5y protein. These 2 hydrogen bonds have distances of 2.03 and 1.72respectively. The dock score was about −11.604, whereas glide and emodel energy were found to be −29.754, −33.251 respectively (**Figure 7**) and (**Table 4**). As rhein has the highest negative value of glide energy, it indicates a stronger binding affinity for MAO-A than all other screened constituents.

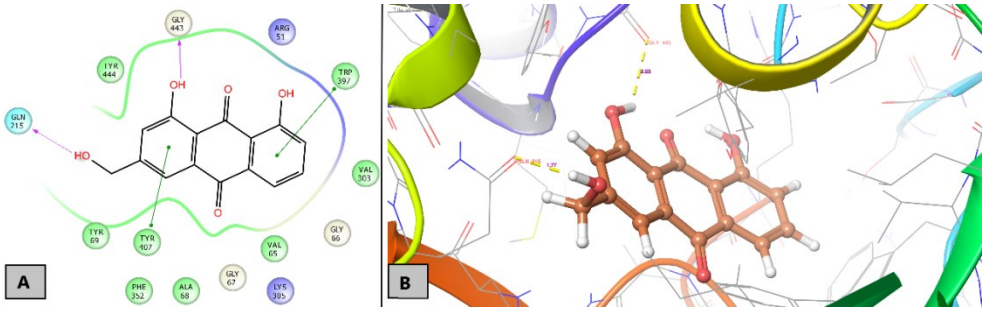

Figure 3 A-aloe-emodin shows binding interactions with GLY (443) and GLN (215) amino acid of MAO-A, 2z5y protein. B-2D representation of aloe-emodin, where it is showing binding interactions with amino acids of MAO-A, 2z5y protein.

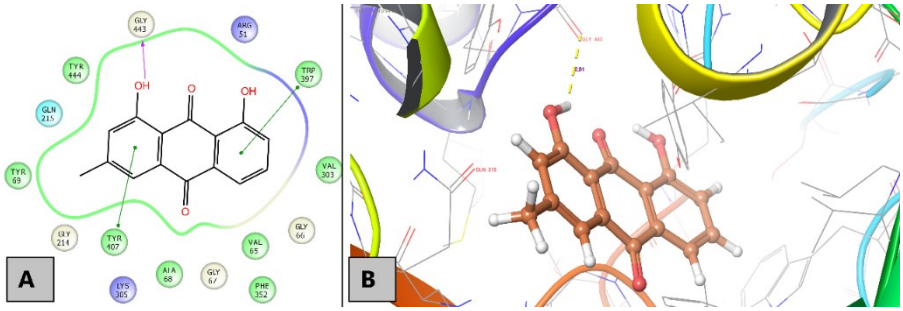

Figure 4 A-chrysophanol shows binding interactions with GLY (443) amino acid of MAO-A, 2z5y protein. B-2D representation of chrysophanol, where it is showing binding interactions with amino acids of MAO-A, 2z5y protein.

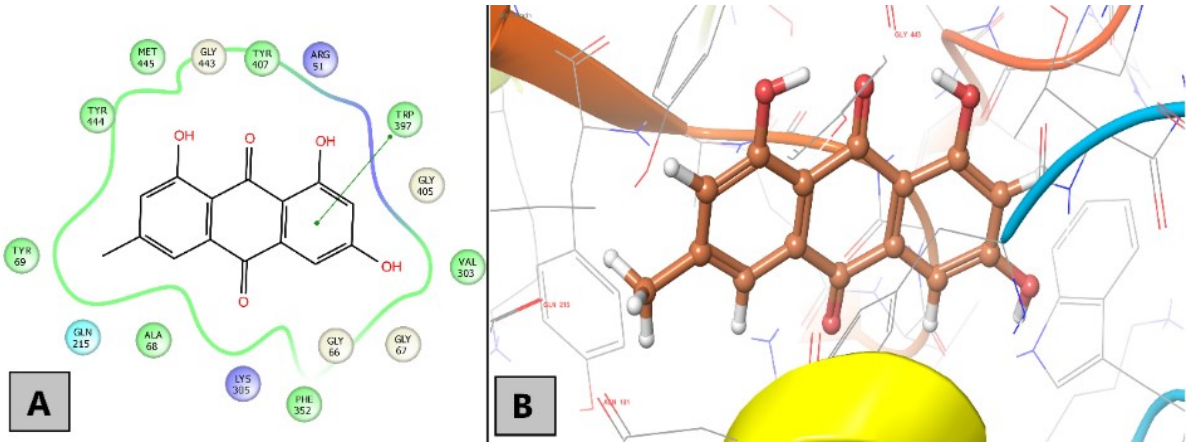

Figure 5 A-emodin does not show binding interactions with amino acids of MAO-A, 2z5y protein. B-2D representation of emodin, where it is not showing binding interactions with amino acids of MAO-A, 2z5y protein.

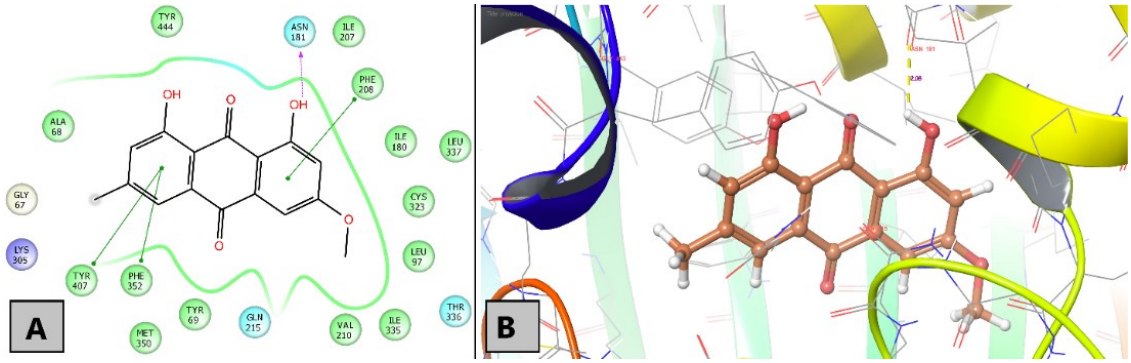

Figure 6 A-physcion shows binding interactions with ASN (181) amino acid of MAO-A, 2z5y protein. B-2D representation of physcion, where it is showing binding interactions with amino acids of MAO-A, 2z5y protein.

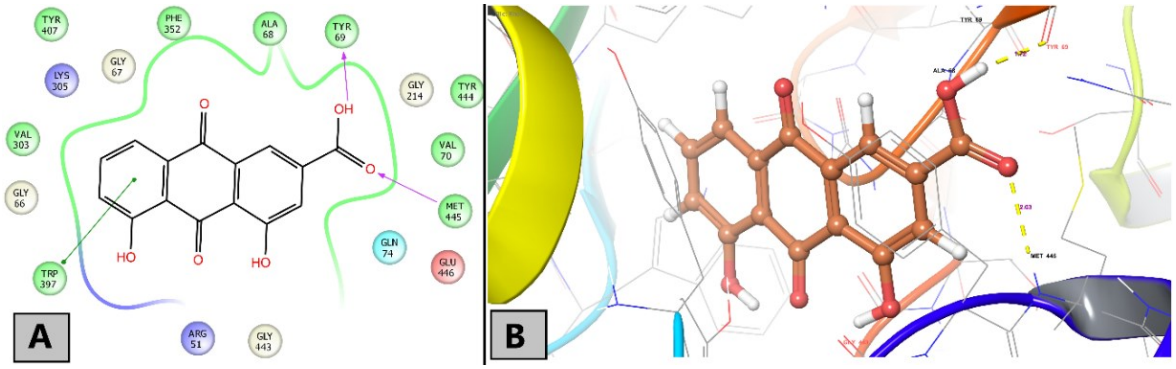

Figure 7 A-Rhein shows binding interactions with MET (445), and TYR (69) amino acid of MAO-A, 2z5y protein. B-2D representation of Rhein, where it is showing binding interactions with amino acids of MAO-A, 2z5y protein.

Table 4 Docking findings and protein-ligand binding interactions of different *R. acetosa* phytoconstituents against MAOA, 2z5y protein.

Compound	Dock score	Number of Hydrogen bonds	Interacting amino acids	Hydrogen bond distance (Å)	Glide energy	Emodel energy
Aloe-emodin	−9.799	2	GLY 443 GLN 215	2.53 1.77	−28.57	−49.107
Chrysophanol	−9.023	1	GLY 443	2.51	−26.099	−41.983
Emodin	−8.439	0	-	-	−22.816	−35.284
Physcion	−8.487	1	ASN 181	2.08	−22.248	−38.407
Rhein	−11.604	2	MET 445 TYR 69	2.03 1.72	−29.754	−33.251

Conclusions

In the present study, therapeutically well-known plant *Rumex acetosa* was extracted, screened for the presence of various phytoconstituents like alkaloids, flavonoids, anthrocyanins etc. Various functional groups were shown by FTIR analysis of the aqueous extract. HPLC and GCMS analysis revealed the presence of various constituents like rhein, aloe emodin, emodin, chrysophanol and physcion. These phytoconstituents are established for *in silico* antidepressant activity against MAO-A. The authors are keenly working on the *in vivo* antidepressant activity of aqueous extract of *Rumex acetosa*. Our research also put forth a way to carry out the isolation of therapeutically proven phytoconstituents and to evaluate these constituents for their biological activity.

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