IJPSR (2023), Volume 14, Issue 3 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 12 July 2022; received in revised form, 26 September 2022; accepted 19 November 2022; published 01 March 2023

UNRAVELING THE PHYTOCONSTITUENTS OF *SCHLEICHERA OLEOSA* AS AN ANTI-ARTHRITIC ACTIVITY: GC-MS ANALYSIS AND MOLECULAR DOCKING STUDIES

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Keywords:

Schleichera oleosa, Rheumatoid arthritis, CHIT1, VCAM-1

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ABSTRACT: Rheumatoid arthritis is a systemic autoimmune and inflammatory disease that primarily affects the synovial joints and eventually destroys them. *Schleichera oleosa* is a plant of Indian provenance that exhibits anti-rheumatoid arthritis activity. The phytochemical constituents in the methanol extract of barks from *Schleichera oleosa* were identified using gas chromatography-mass spectrometry (GC-MS) in the current study. The GC–MS analysis in bark extract identified 21 phytochemical compounds. The PASS server assessed the biological activity of the reported compounds and identified six compounds with anti-arthritic and anti-inflammatory activities. Subsequently, these compounds were screened through ADME/Tox and molecular docking approaches. Two compounds 2,4-Di-tert-butylphenol and 2,6-DI-Tert-butylphenol qualify for all the criteria of ADME/Tox. The molecular docking method identified compounds 2,4-Di-tert-butylphenol and 2,6-DI-Tert-butylphenol had binding affinity ranging between -4.89 to -6.49 kcal/mol with the active site of anti-arthritic target proteins Chitotriosidase-1 and Vascular cell adhesion molecule 1. The findings of this study will create a way to invent herbal medicines for Rheumatoid Arthritis using the *Schleichera oleosa* plant, potentially leading to the development of new drugs.

INTRODUCTION: Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease that can affect numerous tissues and organs but is most commonly associated with synovial joints [1]. RA affects approximately 1% of the world's population, and there is no cure [2]. Rheumatoid arthritis can also produce diffuse inflammation of the lungs, pericardium, pleura, and sclera, as well as nodular lesions, which are most frequent in subcutaneous tissue [3].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.14(3).1312-18

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.14(3).1312-18

Although this disease is prevalent worldwide, its pathogenesis is poorly known [4]. Persistent inflammation causes swollen joints with severe synovitis, a lower nociceptive threshold, and significant sub-synovial infiltration of mononuclear cells, which leads to pannus development and angiogenesis. Pannus enlargement causes bone erosion and cartilage weakening, resulting in joint function loss [5].

The Indian subcontinent is rich in aromatic and medicinal plant flora. This is because India has a diverse range of climatic conditions. Plants with medicinal properties are known to have fewer adverse effects. The Sapindaceae family tree *Schleichera oleosa* (kusum tree) grows in the Himalayan foothills. It is common in many Indian states, including Uttar Pradesh, Madhya Pradesh,

West Bengal, Bihar, and Chhattisgarh. This plant's bark and seed have high pharmacological activity. Central Indian tribes utilize it to relieve arthritis pain and rheumatoid arthritis. Other disorders treated include itching, acne, burns, other skin problems, rheumatism (external massage), hairdressing, and hair growth promotion [6]. The bark is used as an astringent and to treat skin inflammations, ulcers, itching, acne, and other skin diseases [7]. For over three decades, computer-aided drug design has been a popular method for screening, designing, and developing therapeutically useful molecular candidates [8]. These methods combine many approaches, such as molecular docking, ADME (absorption, distribution, metabolism and excretion), and toxicity that aid in the optimization and screening of drugs. Nowadays, another prominent method for determining the interaction between a target protein and small molecule candidates is molecular docking [9]. The approaches can identify promising compounds that can be used in drug design. The ADME specifies pharmacokinetics and pharmacology features, which are critical aspects in the drug design process because they allow us to understand the safety and efficacy of a molecule as a drug candidate. Toxicity analysis is another phase in the drug design process that can be performed using computer tools to determine an undesirable biological effect of a chemical substance or drug candidate. Therefore, the study aimed to identify bioactive compounds from *Schleichera oleosa* by Gas chromatography-mass spectrometry and computational methods that could be used as a therapeutic option for rheumatoid arthritis.

MATERIALS AND METHODS:

Collection of Plant Materials: The plant stem bark sample was collected from Dala Range, Obra Forest Division, Sonbhadra, Uttar Pradesh. The herbarium specimen number of this plant is 7883 [10]. Plant identification and authentication were done with the help of CSIR- National Botanical Research Institute, Lucknow, Uttar Pradesh, India.

Preparation of the Extract: The stem of the plant *Schleichera oleosa* (Lour.) Oken was washed in fresh water thoroughly 2-3 times and once finally with sterile water to remove adhering dust. The stem was then sun-dried for a day, the outer bark of stem was peeled off, and the filling of inner bark was done, and then the grinding of the filled inner bark was done to convert it into powder form. About 2g of the plant bark extract was weighed and placed inside a Soxhlet extractor. A mixture of n-hexane and methanol (50/50) v/v was placed within a round-bottom flask. The flask was attached to the main Soxhlet extractor, and the condenser was attached to the extractor, which was connected to a pipe with a continuous water flow. The extractor was heated using a heating chamber for about 2–3 h. The solvent was run through the tumble containing the sample, which traps all the possible extract into the solvent inside the round bottom flask. The extract was then cleaned by passing it through a column packed with silica gel that had already been saturated with methanol. The extract was dried using hydrous sodium sulphate. The cleaned extract was then concentrated to about 1 ml using nitrogen concentration before being introduced into the GC-MS analyzer.

Gas Chromatography-mass Spectrometry (GC-MS) Analysis: The gas chromatography-mass spectrometry (GC-MS) analysis of the bark *Schleichera oleosa* was performed using a GC-MS (Modal; Agilent technologies 7890A) equipped with a VF -5 ms fused silica capillary column of 30 m length, 0.25 mm diameter and 0.25 mm film thickness. An electron ionization system with an ionization energy of 70eV was used for GC-MS detection. Helium gas (99.99%) was used as a carrier gas at a constant flow rate of 1 ml/min. Injection and mass transfer line temperatures were set at 200 and 240 °C, respectively.

The oven temperature was programmed from 80 °C to hold for 2 mins@ 10 °C/min to 240 °C to hold for 6 mins. 2 ml of water solution of the samples was manually inserted in the split less mode, with a split ratio of 1:40 and with a mass scan of 50–600 amu. The total running time of the GC-MS was 35 min. The relative percentage of each extract constituent was expressed as a percentage with peak area normalization. The plant extract's mass spectrum was interpreted using the database of the National Institute of Standard and Technology (NIST) library, having more than 62,000 spectral patterns. The spectra of the compounds were compared with the spectra of the National Institute of Standard and Technology (NIST) library database.

Prediction of the Biological Activity of Compounds: The compounds were submitted to the Pass online server, which detects the biological activity of compounds [11]. Its assistance was used to identify compounds with biological activity against Rheumatoid Arthritis.

Ligand Preparation: A review of the literature revealed that small molecules extracted from the inner bark of the plant *Schleichera oleosa* have anti-arthritic and anti-inflammatory activities. So, after Soxhlet extraction, the isolated bioactive compounds were subjected to the GC-MS method for identification. The 2D structure of identified compounds by GC-MS method was drawn using the PubChem Sketcher V2.4 (https://pubchem.ncbi.nlm.nih.gov//edit3/index.html). Open Babel was used to converting 2D to 3D structure of identified compounds [12].

***In-silico* ADME/Tox Prediction of Compounds:** *In-silico* physicochemical, drug-likeness, and pharmacokinetics of identified bioactive compounds were predicted by the Swiss ADME web tool [13]. The Pre ADMET tool was used to assess the toxicological properties of compounds [14].

Protein Preparation: Chitotriosidase (CHIT1) is a widely secreted protein mostly generated by activated macrophages and epithelial cells. Serum chitotriosidase levels were considerably higher in rheumatoid arthritis patients [15]. Vascular Cell Adhesion Molecule-1 (VCAM-1) expression is closely associated with rheumatoid arthritis. Wang et al. discovered that serum VCAM-1 level was significantly higher in RA patients than in controls and that long-term use of aspirin decreased serum levels of rheumatoid factor and VCAM-1, suggesting that serum VCAM-1 level may be related to disease severity [16].

Crystal structure of human chitinase in complex with allosamidin (PDB Id: 1HKK) and Integrin-binding fragment of Vascular Cell Adhesion Molecule-1 (PDB Id: 1VCA) was retrieved from the Protein Data Bank (https://www.rcsb.org/). All the heteroatoms were removed, and polar hydrogen was added to proteins for the molecular docking process.

Molecular Docking: Binding site residues of Chitotriosidase-1 and Vascular Cell Adhesion Molecule-1 were retrieved from literature [17, 18]. Docking was done on the MTi Open Screen server using AutoDock implemented in MTiAutoDock [19]. Docking results were visualized using Python Molecular Viewer tool to show the 3D structure and position of compound binding to the protein [20].

RESULTS AND DISCUSSION: The GC-MS analysis was performed to identify the bioactive compounds in *Schleichera oleosa* bark methanol extract. GC-MS chromatogram of methanol extract of bark parts of *Schleichera oleosa* is shown in **Fig. 1**. A total of 21 bioactive compounds were obtained based on NIST libraries.

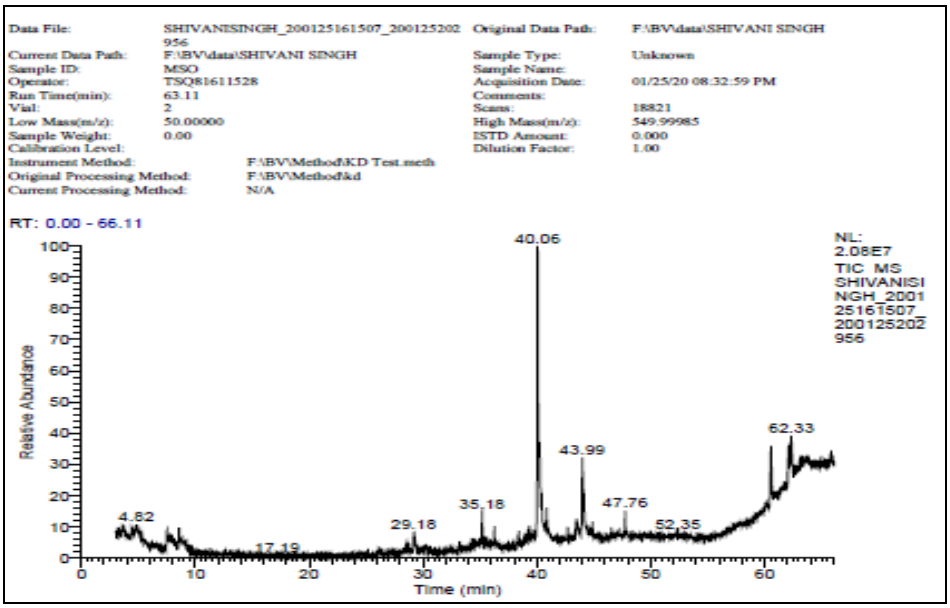
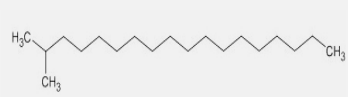
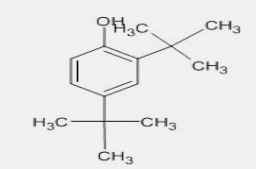
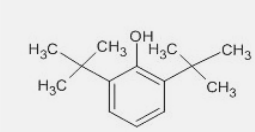
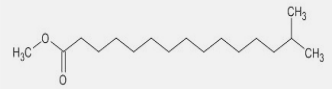
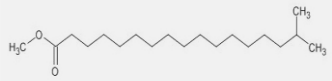


FIG. 1: GC-MS CHROMATOGRAM FOR METHANOL EXTRACT OF BARK PARTS OF *SCHLEICHERA OLEOSA*

The PASS server was used to predict the biological activity of identified 21 compounds by GC-MS analysis. These 6 compounds were found to have anti-arthritic activity, as shown in **Table 1.**

TABLE 1: BIOLOGICAL ACTIVITY OF COMPOUNDS IDENTIFIED FROM BARK OF *SCHLEICHERA OLEOSA*

Sl. no.	Ligand structure	Molecular formula	Name	Probability	Biological Activity
1		$C_{21}H_{44}$	2-Methyleicosane	4.95	Antiarthritic, anti-inflammatory, antineurotic, antiviral
2		$C_{19}H_{40}$	2-methyl Octadecane	2.98	Antiarthritic, anticarcinogenic, anti-inflammatory
3		$C_{14}H_{22}O$	2,4-Di-tert-butylphenol	30.15	Antiarthritic, antiasthmatic, anticarcinogenic, anti-inflammatory
4		$C_{14}H_{22}O$	2,6-Di-Tert-butylphenol	23.70	Antiarthritic, anticarcinogenic, antidiabetic, anti-inflammatory
5		$C_{17}H_{34}O_2$	Methyl 14-methylpentadecanoate	12.29	Antiarthritic, anticarcinogenic, antidiabetic, anti-inflammatory
6		$C_{19}H_{38}O_2$	Methyl isostearate	28.21	Antiarthritic, antibacterial, anticarcinogenic, anti-inflammatory

ADME/Tox Analysis of Compounds: The Physicochemical and drug-likeness properties of six compounds were shown in **Table 2**. Compounds were accessed by Lipinski rule-of-five [21]. **Table 3** shows the ADME predictions for compounds for human gastrointestinal absorption (GI) and blood-brain barrier (BBB) penetration. The features of human intestine absorption are a determinant of drug synthesis and must be supplied orally. BBB plays a significant role in the pharmacology of drugs [22]. The result presented in **Table 2** shows that compounds 2, 4-Di-tert-butylphenol, 2, 6-Di-Tert-butylphenol and Methyl 14-methylpentadecanoate have high gastro-intestinal absorption and good BBB. Methyl 14-methylpentadecanoate is toxic as shown in **Table 3**. At the end of the entire ADME/Tox evaluation screening, two compounds 2,4-Di-tert-butylphenol and 2,6-Di-Tert-butylphenol satisfied all the criteria.

TABLE 2: THE PHYSICOCHEMICAL PROPERTIES AND DRUG-LIKENESS PREDICTION OF COMPOUNDS

Sl. no.	Ligand Name	Physicochemical					Druglikeness	
		nRot	HBA	HBD	TPSA (Å²)	MW g/mol	Bioavaliab-ility Score	Lipinski Rule
1	2-Methyleicosane	17	0	0	0.00	296.57	0.55	Yes
2	2-Methyl Octadecane	15	0	0	0.00	268.52	0.55	Yes
3	2,4-Di-tert-butylphenol	2	1	1	23.06	206.32	0.85	Yes
4	2,6-Di-Tert-butylphenol	2	1	1	23.06	206.32	0.85	Yes
5	Methyl 14-methylpentadecanoate	14	2	0	26.30	270.45	0.55	Yes
6	Methyl isostearate	16	2	0	26.30	298.50	0.55	Yes

nRot: Number of rotatable bonds, HBA: Hydrogen bond acceptor, TPSA: Topological polar surface area, MW: Molecular weight.

TABLE 3: THE PHARMACOKINETICS AND CARCINOGENICITY PREDICTION OF COMPOUNDS

Sl. no.	Ligand Name	Pharmacokinetics			Carcinogenicity		
		GI	BBB	Log Kp (cm/s)	Ames test	Mouse	Rat
1	2-Methyleicosane	Low	No	-0.09	mutagen	-ve	+ve
2	2-Methyl Octadecane	Low	No	-0.68	mutagen	-ve	+ve
3	2,4-Di-tert-butylphenol	High	Yes	-3.87	non-mutagen	-ve	-ve
4	2,6-Di-Tert-butylphenol	High	Yes	-4.07	non-mutagen	-ve	-ve
5	Methyl 14-methylpentadecanoate	High	Yes	-2.84	non-mutagen	+ve	+ve
6	Methyl isostearate	High	No	-2.32	non-mutagen	+ve	+ve

GI: Gastrointestinal absorption, BBB: Blood brain barrier penetration, Log Kp-Skin Permeation Coefficient.

Analysis of Molecular Docking: Active site of Chitotriosidase-1 (PDB ID: 1HKK) was retrieved from the PDB sum. Chitotriosidase-1 active site residues were taken with the centroid of the residues for constructing the receptor grid box, taking into account the following amino acids: Tyr267(A), Asp213(A), Trp358(A), Tyr212(A), Met210(A), Trp99(A), Asp138(A), Gly98(A), Phe58(A), Ala183(A), Glu140(A), Tyr27(A), Met356(A). Integrin-binding motif (Q38IDSPL) of Vascular Cell Adhesion Molecule-1 was used as binding site residues for docking studies. The position of the grid box can be adjusted to cover the entire binding site residues GLN38, ILE39, ASP40, SER41, PRO42, LEU43 and LYS46 of VCAM-1 protein. 2,4-Di-tert-butylphenol and 2,6-DI-Tert-butylphenol were docked in the binding site of Chitotriosidase-1 (CHIT1) and Vascular cell adhesion molecule 1 (VCAM-1) (PDB Id: 1VCA) using MTiAutoDock server. The docking results of compounds with CHIT1 and VCAM-1 proteins were shown in **Table 4.**

TABLE 4: DOCKING RESULTS OF COMPOUNDS WITH CHIT1 AND VCAM-1 PROTEIN

Sl. no.	Compound Name	CHIT1 (kcal/mol)	VCAM-1 (kcal/mol)
1	2,4-Di-tert-butylphenol	-6.49	-5.52
2	2,6-Di-Tert-butylphenol	-6.34	-4.89

On analysis of the binding energy of compounds, it was found that these had a low binding affinity with CHIT1 and VCAM-1 proteins **Table 3**. Predicted docked complexes were analyzed through Python Molecular Viewer for their interaction study shown in **Fig. 2** & **3**. Compounds were represented in sticks model. 2, 4-Di-tert-butylphenol interacted with residues GLY98, TRP99, GLU140, ASP138, PHE58, TRP31, TRP358, TYR212 and MET210 of CHIT1 protein **Fig. 2A**. 2, 4-Di-tert-butylphenol also interacted with residues SER34, TRP35, PHE33, LEU43 and VAL47 of VCAM-1 protein **Fig. 2B**. 2, 6-Di-tert-butylphenol interacted with residues GLU140, TRP99, ASN100, PHE58, TRP31, TRP358 and TYR212 of CHIT1 protein **Fig. 3A**. 2, 6-Di-tert-butylphenol also interacted with residues SER34, TRP35, PHE33, LEU43 and VAL47 of VCAM-1 protein **Fig. 3B.**

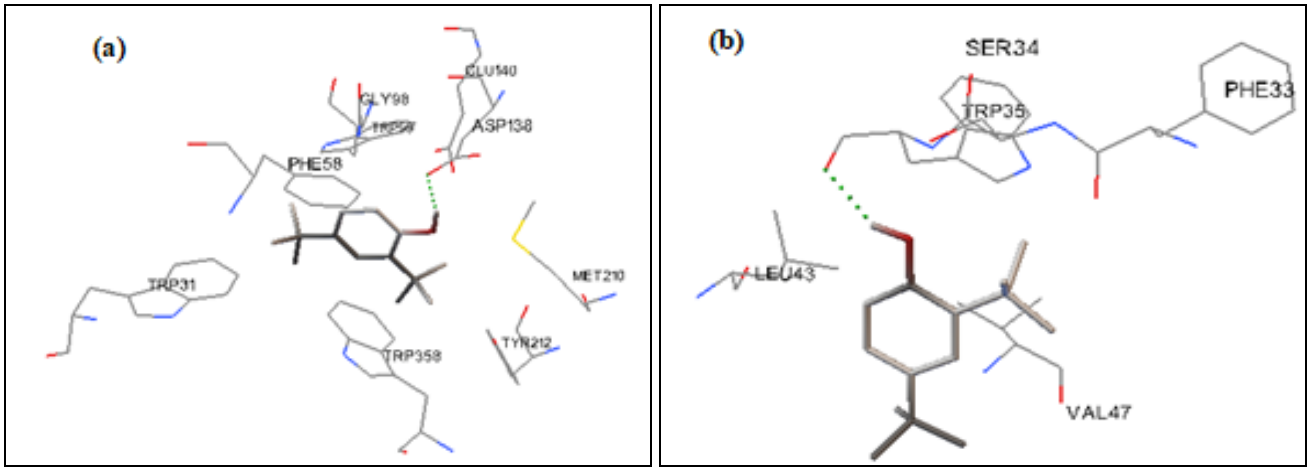


FIG. 2: (A) DOCKING POSE OF 2, 4-DI-TERT-BUTYLPHENOL IN BINDING SITE OF CHIT1 PROTEIN. (B) DOCKING POSE OF 2, 4-DI-TERT-BUTYLPHENOL IN BINDING SITE OF VCAM-1 PROTEIN

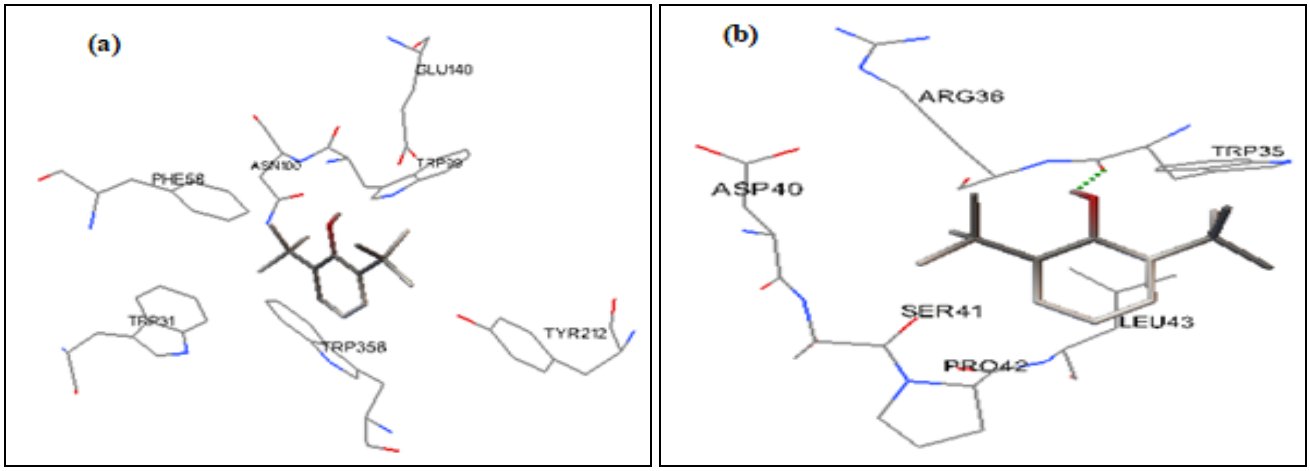


FIG. 3: (A) DOCKING POSE OF 2,6-DI-TERT-BUTYLPHENOL IN BINDING SITE OF CHIT1 PROTEIN. (B) DOCKING POSE OF 2,6-DI-TERT-BUTYLPHENOL IN BINDING SITE OF VCAM-1 PROTEIN. ONE H-BOND WAS FORMED BETWEEN AMINO ACID TRP35 OF PROTEIN WITH COMPOUND, RESPECTIVELY. THE HYDROGEN BOND IS REPRESENTED WITH SPHERICAL LINE

Plants have been used as a source of medicine for centuries and are an essential component of the Indian healthcare system. It has been reported that the bark of the *Schleichera oleosa* plant contains antibacterial, antiarthritic, antioxidant and anticancer properties, as well as phytochemicals such as terpenoids, betulin and betulinic acid [23]. Kaur *et al.* (2012) reported on various herbs and plants with anti-arthritic and anti-inflammatory characteristics for reducing joint pain and inflammation in RA [24]. Currently, nonsteroidal anti-inflammatory drugs, corticosteroids, disease-modifying anti-rheumatic medicines, and biological agents are employed in treating RA [25]. However, taking these drugs together may cause constipation [26], stomach ulcer [27], dizziness, headaches, and dyspepsia [28]. Therefore, exploration continues for alternative products and natural phytochemicals from medicinal plants with lesser side effects.

CONCLUSION: The identification of bioactive compounds in *Schleichera oleosa* was done by GC-MS analysis, which shows the presence of 21 compounds. Among the identified compounds, 2,4-Di-tert-butylphenol and 2,6-Di-Tert-butylphenol have a role in anti-arthritic and anti-inflammatory activity. In molecular docking experiments, these compounds also showed promising binding affinity toward RA target proteins CHIT1 and VCAM-1. From this study, it can be concluded that *Schleichera oleosa* may serve as a new potential source of drugs for Rheumatoid arthritis due to the presence of these bioactive compounds.

ACKNOWLEDGMENT: The authors extend heartfelt gratitude to the Guides and gratefully acknowledge the cooperation of the faculty of Biotechnology, Shri Ramswaroop Memorial University, Lucknow-Deva Road, Barabanki, India.

CONFLICTS OF INTEREST: The authors declare no conflict of interest.

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How to cite this article:
Singh S, Paliwal S, Qidwai T and Singh S: Unraveling the phytoconstituents of *Schleichera oleosa* as an anti-arthritic activity: GC-MS analysis and molecular docking studies. Int J Pharm Sci & Res 2023; 14(3): 1312-18. doi: 10.13040/IJPSR.0975-8232.14(3).1312-18.