

Research Article***In-Silico* & Biological Activity Evaluation of Herbal and Synthetic Compound for the Treatment of Arthritis: A comparative ADMET Analysis**

Snnehaa Bhosle^{1*}, Komal Laddha², Dr. Meera Deshmukh³, Dr. Pranati Tilak⁴

¹Assistant Professor, Pharmacy Department, Tilak Maharashtra Vidyapeeth's Lokmanya Tilak Institute of Pharmaceutical Sciences, Pune - 411037

²Assistant Professor, Pharmacy Department, Tilak Maharashtra Vidyapeeth's Lokmanya Tilak Institute of Pharmaceutical Sciences, Pune - 411037

³Registrar, Tilak Maharashtra Vidyapeeth's Lokmanya Tilak Institute of Pharmaceutical Sciences, Pune - 411037

⁴Director, Tilak Maharashtra Vidyapeeth's Lokmanya Tilak Institute of Pharmaceutical Sciences, Pune - 411037

***Corresponding Author:**

Snnehaa Bhosle

Pharmacy Department,

Tilak Maharashtra Vidyapeeth's Lokmanya Tilak Institute of Pharmaceutical Sciences, Pune - 411037

Abstract: This study evaluates the potential of natural phytoconstituents Curcumin, Boswellic acid, Linoleic acid, and Colchicine derived from herbal remedies used in the treatment of Rheumatoid Arthritis (RA), and compares them with the synthetic drug Methotrexate. Using in-silico tools such as ADMETlab 3.0, PubChem, and Molinspiration, the compounds were analysed for their pharmacokinetic (ADMET) properties and biological activity. Results showed that the natural compounds exhibited good absorption, enzyme inhibition potential, and lower toxicity profiles compared to Methotrexate, which, despite its effectiveness, showed higher toxicity. The findings suggest that natural phytoconstituents, particularly Curcumin, could serve as safer and effective alternatives in RA therapy.

Keywords: Rheumatoid Arthritis, Methotrexate, ADMETlab 3.0, PubChem, and Molinspiration

1. Introduction

As we know natural drugs have much less adverse drug reaction (ADRs) compared to synthetic drugs, but no natural drug is free from side effects. They have some ADRs but most of the time they are negligible. Therefore, many times natural herbs are preferred. From ancient times herbal drugs are used in Ayurvedic system of medicine but these drugs also need to be evaluated.

For this purpose, we have evaluated 'Curcumin' via in-silico method. The fields of science and medicine as well as cooking have both shown a great deal of interest in turmeric. *Curcuma longa*, a perennial herbaceous plant, belongs to the ginger family and is Rhizomatous known by the name diferuloylmethane, curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) is the primary naturally occurring polyphenol present in the rhizome of *Curcuma longa*, or turmeric, as well as other *Curcuma* spp. Asian nations have long utilized *curcuma longa* as a medicinal herb because of its anticancer, antibacterial, antimutagenic, antioxidant, and anti-inflammatory qualities.^[1]

It's common knowledge that early assessment of a chemical's absorption, distribution, metabolism, excretion, and toxicity (ADMET) is essential. To properly and thoroughly assess the physicochemical properties of molecules and the ADMET. For the ADMET evaluation we have used ADMETlab 3.0.

Lipinski's rule of five:

Often referred to as Pfizer's rule of five or just the rule of five (RO5), Lipinski's rule of five is a general guideline for assessing drug likeness, or whether a

chemical compound with a particular pharmacological or biological activity possesses the chemical and physical characteristics that would likely make it an oral active drug in humans. Christopher A. Lipinski developed the rule in 1997 after seeing that the majority of medications taken orally are tiny, somewhat lipophilic compounds. [2]

The rule was proposed by Christopher A. Lipinski in 1997 and consists of the following key criteria:

- 1 Molecular weight: Less than 500 Dalton.
- 2 Octanol-water partition coefficient (log P): Less than 5. This measures a molecule's lipophilicity (fat-solubility).
- 3 Hydrogen bond donors: No more than 5 (i.e., the number of NH and OH groups).
- 4 Hydrogen bond acceptors: No more than 10 (i.e., the number of N and O atoms that can accept hydrogen bonds).

These guidelines are not strict rules but serve as general parameters to help chemists design molecules with good pharmacological properties. However, there are exceptions, and some drugs may still work well even if they violate one or more of these rules. [3]

The objective of Lipinski's Rule of Five is to help predict the oral bioavailability of a compound by identifying whether a drug-like molecule has properties that are favourable for absorption, distribution, metabolism, and excretion (ADME). The rule provides a quick, computational method to assess the likelihood of a molecule being effective as an orally administered drug.

Various Natural Drugs Used in Rheumatoid Arthritis

1] Turmeric

Curcumin is the primary active ingredient of turmeric, along with desmethoxycurcumin, bisdemethoxycurcumin, and other curcuminoids. In 1815, curcumin was initially separated from turmeric. Turmeric's yellow colour is attributed to curcumin, which is also responsible for most of its medicinal properties. [5]The autoimmune illness rheumatoid arthritis (RA) primarily affects the joints and is chronic (long-lasting). When the immune system, which often aids in defending the body against illness and infection, targets its own tissues, RA results. Joint discomfort, oedema, stiffness, and loss of function are all symptoms of the condition.



Figure1-Tumeric

Use of Curcumin is done in treatment of RA in recent years. By inhibiting the COX-2 pathway and activating NF-kB, curcumin contributes to an anti-inflammatory response. Curcumin may have anti-inflammatory, antioxidant, anti-diabetic, and anti-cancer effects, according to a number of research conducted in more recent years. Curcumin affects the activity of enzymes, receptors, and transcription factors, among other targets, according to these studies, and its modes of action vary. Furthermore, practically no negative effects have been documented with curcumin administration, suggesting it as a possible substitute for NSAIDs and other drugs known to have serious side effects. It will be easier to assess how curcumin exerts its therapeutic potential via distinct modes of action in a variety of disease processes if all data from various rheumatic diseases are examined. Studies on the effectiveness of curcumin in treating osteoarthritis (OA), ulcerative colitis (UC), type 2 diabetes mellitus (T2DM), rheumatoid arthritis (RA), lupus nephritis (LN), and multiple sclerosis (MS) are reviewed in this article. [6]

2] Boswellia:

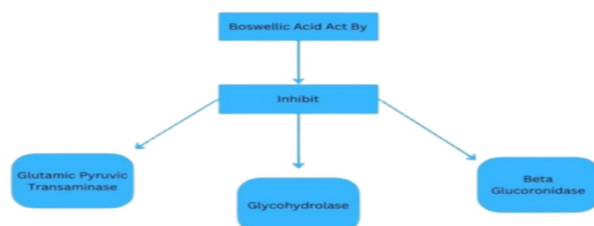
Boswellia serrata, also known as Salai or Salai guggul, is a moderately to big, branched tree belonging to the *Boswellia* genus in the family Burseraceae. *Boswellia serrata* gum-resin extracts have been used in traditional medicine to treat a range of chronic inflammatory conditions for millennia.



Figure 2- Boswellia serrata

The resinous portion of *Boswellia serrata* contains four major pentacyclic triterpene acids, namely β -boswellic acid, acetyl- β -boswellic acid, 11-keto- β -boswellic acid, and acetyl-11-keto- β -boswellic acid, which are responsible for inhibiting pro-inflammatory enzymes. [7]

Boswellic acid act to reduce following three enzymes associated with RA [8]



3] Rosehip:

The fruits of the rose bush (rose plant) in the Rosaceae family's *Rosa* genus are called rose hips. Three major bioactive fatty acid phytoconstituents 1) a galactolipid, 2) linoleic acid (a ω -6 polyunsaturated FA [PUFA]), and 3) α -linolenic acid (a ω -3 PUFA). All three substances have demonstrated anti-inflammatory qualities.^{5–7} Furthermore, in vitro studies have demonstrated the chondroprotective potential of galactolipids. ^[9]



Figure 3- Rosehip

The mechanism by which Rosehip show action is as following. [10]

Linoleic Acid



Inhibits NF-kB Signaling



Reduces Activation of Pro-inflammatory Genes



Inhibits Pro-inflammatory Enzymes (e.g., COX-2, iNOS)



Decreased Production of Inflammatory Mediators (e.g., Prostaglandins, Nitric Oxide)



Reduced Inflammatory Response.

4] Colchicum:

Colchicum, a member of the Liliaceae family, is made up of dried, ripe seeds and corms of *Colchicum autumnal* Linn. Medicinal plants in the genus *Colchicum* contain significant amounts of phenolics and bioactive alkaloids, primarily colchicine. ^[11] Colchicine acts by many pathways to give anti-inflammatory action. ^[12]



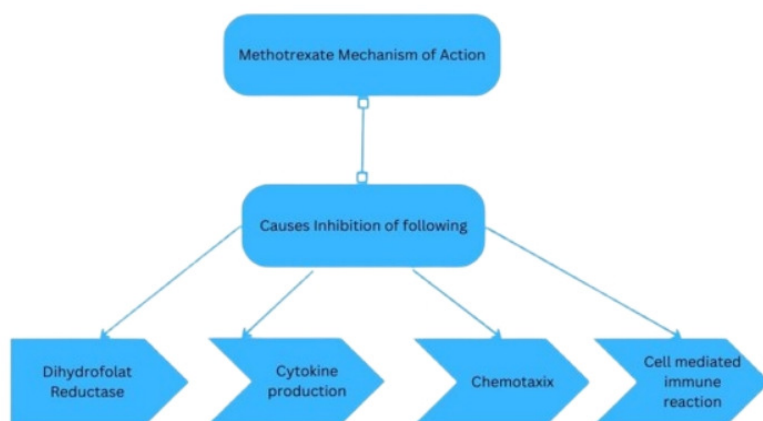
Figure 4-Colchicum

5] Synthetic Drug: -Methotrexates

A common folic acid antagonist used to treat neoplastic diseases is methotrexate. By binding to dihydrofolate reductase, methotrexate prevents the creation of proteins, ribonucleic acid (RNA), and deoxyribonucleic acid (DNA). One of the most widely prescribed medications for the treatment of rheumatoid arthritis (RA) now is methotrexate. ^[13]

Methotrexate is a dihydrofolate reductase inhibitor. It shows anti-inflammatory and immunosuppression action.

The probable mechanism related with RA is as follows. ^[14]



Phytoconstituents Evaluated:

1. Turmeric:- Curcumin
2. Boswellia :- Boswellic Acid
3. Rosehip:- Linoleic Acid
4. Colchicum:- Colchicine

Materials and Methods:

1] PUBCHEM

The world's largest available chemical information database is called PubChem. Chemicals can be found using their names, structures, molecular formulas, and other identifiers. Discover information about biological activity, safety and toxicity, chemical and physical qualities, patents, literature citations, and more. We have taken canonical smiles from PubChem and these smiles were put in ADMETlab 3.0 software to study ADMET toxicity studies

2] ADMETlab 3.0

The canonical smiles structure was put in this software to obtain ADMET studies for evaluation.

3 RESULT

1 Physicochemical Property and Medicinal Chemistry ¹⁵

Table 1:

Drugs	Number of Hydrogen Bond Donor	Number of Hydrogen Bond Acceptor	LOG P	LOG S	QED	Lipinski Rule	Molecular Weight	Volume
Curcumin	0.0	5.0	2.801	-4.148	0.455	Accepted	318.1	316.597
Boswellic acid	2.0	3.0	4.27	-5.183	0.414	Accepted	456.36	505.751
Colchicine	1.0	7.0	0.661	-2.275	0.833	Accepted	399.17	406.045
Linoleic Acid	0.0	1.0	3.543	-3.176	0.65	Accepted	280.24	257.684
Methotrexate	7.0	13.0	-2.163	-3.938	0.295	Accepted	454.17	431.731

1. Number of Hydrogen Bond Donor: - Optimal: 0-7
2. Number of Hydrogen Bond Acceptors: Optimal: 0-12
3. Log P: The logarithm of the water distribution coefficient at pH 7

Log P value of Methotrexate is -2.163 which is lowest amongst all which means it is highly lipophilic in nature and has more tissue permeability than others.

The order of lipophilicity:

Methotrexate>Colchicine>Curcumin>Linoleic Acid>Boswellic Acid

2 Absorption

Table2: Absorption related factors ¹⁶

Drugs	Caco-2 Permeability	MDCK Permeability	Pgp inhibitor	HIA
Curcumin	-5.417	0.0	Excellent	Excellent
Boswellic Acid	-5.362	0.0	Excellent	Excellent
Colchicine	-4.797	-4.705	Medium	Excellent
Linoleic Acid	-5.062	0.0	Excellent	Excellent
Methotrexate	-5.957	-5.249	Excellent	Excellent

1 Caco-2 Permeability: It is used to measure the intestinal permeability. It is used to predict in-vivo absorption of drugs. >5.15 is excellent, except Colchicine all have excellent permeability.

2 MDCK Permeability: Madin Darby Canine Kidney Cells (MDCK) is developed as an in vitro model for permeability screening. Curcumin, Boswellic acid, and Linoleic acid have good MDCK permeability whereas Colchicine and Methotrexate have poor permeability.

3 Pgp Inhibitor: Optimal values are; 0.3-0.7

Except Colchicine all others have excellent Pgp inhibition properties.

4 HIA; Human Intestinal Absorption

It is an important factor for oral drug absorption, as it affects oral drug efficacy. There is a close relation between oral bioavailability and intestinal absorption. All drugs have excellent HIA.

3 Distribution

Table 3: - Distribution related factors:

Drugs	PPB	BBB	VD
Curcumin	90.9%	-	0.299
Boswellic Acid	88.3%	-	0.53
Colchicine	92.718%	0.075	0.583
Linoleic Acid	97.0%	-	0.615
Methotrexate	47.354	0.0	-0.366

1 PPB: Plasma Protein Binding ¹⁷

It is one of the major mechanisms for distribution and drug uptake. It has a significant effect on the pharmacodynamic parameters of drug.

PPB of <90% is optimal. As we can see Methotrexate and Boswellic acid have excellent PPB.

2 BBB: Blood Brain Barrier

Drug that needs to show CNS effects need to cross BBB and drugs with less BBB distribution are intended for minimal CNS side effects.

Only Colchicine and Methotrexate cross BBB

3 VD: Volume of Distribution

It is a theoretical concept that provide dose administered with the actual concentration of the the drug in system circulation. It is an important parameter for in vivo distribution of the drug

The optimal value is 0.04-20L/kg

Boswellic acid, Colchicine, and linoleic acid have excellent VD

4 Excretion

Table 4: Excretion related factors

Drugs	T1/2	Clearance
Curcumin	1.196	9.635
Boswellic Acid	1.376	3.778
Colchicine	2.004	1.088
Linoleic Acid	0.598	3.804
Methotrexate	2.926	1.975

1) $t_{1/2}$: Half Life:

Half-life is the concept that involves clearance and VD.

Short $t_{1/2}$: 1-4 hrs

Intermediates $t_{1/2}$: 4-8 hrs

Long $t_{1/2}$: >8 hrs

All the drugs have a short half-life.

2) Clearance:

Clearance is one of the important pharmacokinetic parameters.

High Clearance : >15 ml/min/kg

Moderate Clearance: 5-15 ml/min/kg

Low Clearance: <5 ml/min/kg

Except for Curcumin all other drugs have low clearance which means that they show a longer duration of action.

5 Toxicophore Rule

Table 5: Various toxicophore rules

Drugs	Acute Toxicity Rule	Skin Sensitisation Rule	Aquatic Toxicity Rule	Non Bio degradable Rule
Curcumin	2	8	0	1
Boswellic Acid	1	0	0	0
Colchicine	0	2	0	0
Linoleic Acid	0	0	0	0
Methotrexate	0	3	0	1

From the above data, we can conclude that Curcumin and Methotrexate have high toxicity compared to other drugs.

6. Toxicity:

Table 6: - Toxicity related factors. ¹⁸

Drugs	Rat Oral Acute Toxicity	Carcinogenicity	Eye Irritation	Respiratory	Genotoxicity
Curcumin	0.177	0.124	0.863	0.744	0.015
Boswellic Acid	0.083	0.464	0.057	0.688	0.001
Colchicine	0.563	0.566	0.017	0.957	1.0
Linoleic acid	0.064	0.1	0.999	0.706	0.0
Methotrexate	0.369	0.465	0.006	0.51	1.0

1 Rat Oral Acute Toxicity:

It is one of the important safety evaluations for drug candidates.

Values:

Excellent :0-0.3

Medium: 0.3-0.7

Poor: 0.7-1.0

Curcumin , Boswellic acid and Linoleic acid have excellent values.

2 Carcinogenicity:

It is of great concern because it greatly affects human health

Values:

Excellent: 0-0.3

Medium: 0.3-0.7

Poor: 0.7-1.0

Curcumin and linoleic acid have excellent values.

3 Eye Irritation:

Eye Irritation potential evaluation of a drug is an essential component of risk assessment.

Values:

Excellent: 0-0.3

Medium: 0.3-0.7

Poor: 0.7-1.0

Curcumin and linoleic acid have poor eye irritation values.

4. Respiratory Toxicity:

Among this toxicity respiratory toxicity has become the main cause of drug withdrawal

All the drugs have medium to poor respiratory toxicity values.

5. Genotoxicity:

Category 0: Non genotoxic

Category 1: Genotoxic

PREDICTION OF BIOLOGICAL ACTIVITY USING MOLINSPIRATION SOFTWARE

Molinspiration is a computational in-silico tool widely used in drug discovery and cheminformatics to predict the biological activity of small molecules based on their chemical structure. The software uses SMILES (Simplified Molecular Input Line Entry System) — a linear text notation of a chemical structure — to calculate bioactivity scores across six key target classes relevant to pharmaceutical development.

These predictions help researchers determine if a molecule is likely to interact with a specific class of biological targets, which is useful in identifying potential drug candidates.

Each score reflects the likelihood of a compound to act as a modulator or inhibitor of the respective target. Here's a breakdown of what each target type represents:

Target Class	Full Name	Description
GPCR ligand (GPCR)	G Protein-Coupled Receptor Ligand	Predicts if the molecule can act on GPCRs, a large protein family involved in signal transduction, targeted by many drugs for pain, inflammation, cardiovascular diseases.
Ion Channel Modulator (ICM)	Ion Channel Modulator	Predicts interaction with ion channels that regulate ion flow across membranes, crucial in nerve signal transmission, cardiac rhythm, and muscle contraction.
Kinase Inhibitor (KI)	Kinase Inhibitor	Indicates if a compound might inhibit protein kinases, enzymes that regulate cell signaling and are often targeted in cancer therapy.
Nuclear Receptor Ligand (NRL)	Nuclear Receptor Ligand	Predicts the ability to interact with nuclear hormone receptors (e.g., estrogen, glucocorticoid receptors), which regulate gene expression. Important in metabolic and endocrine disorders.
Protease Inhibitor (PI)	Protease Inhibitor	Suggests whether the compound can inhibit proteases, enzymes that break down proteins. Protease inhibitors are important in viral infections (e.g., HIV) and inflammation.
Enzyme Inhibitor (EI)	Enzyme Inhibitor	General prediction for inhibition of enzymes involved in metabolism, inflammation, or

		microbial survival. Many traditional drugs fall in this class.
--	--	--

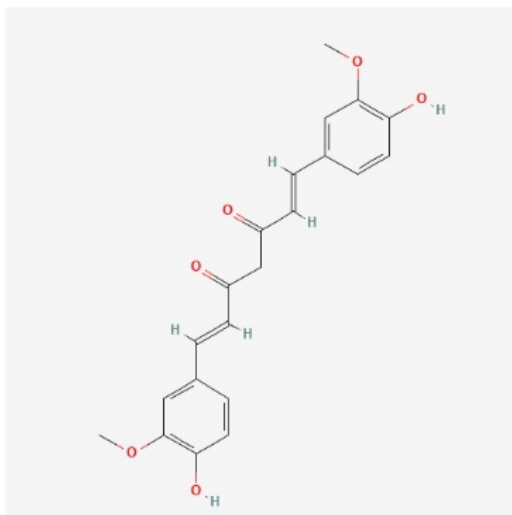
Bioactivity Score Interpretation

Molinspiration assigns a **numerical score** for each activity class, based on molecular properties such as:

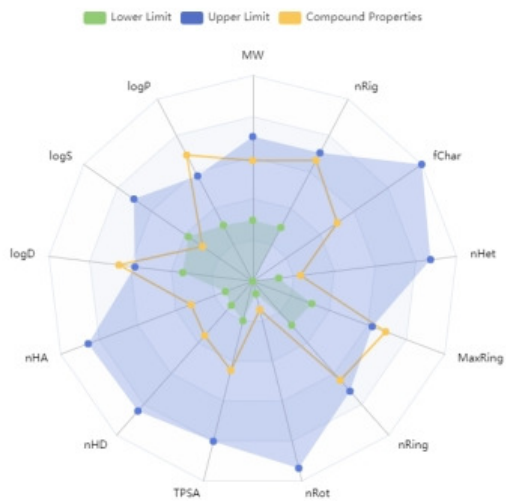
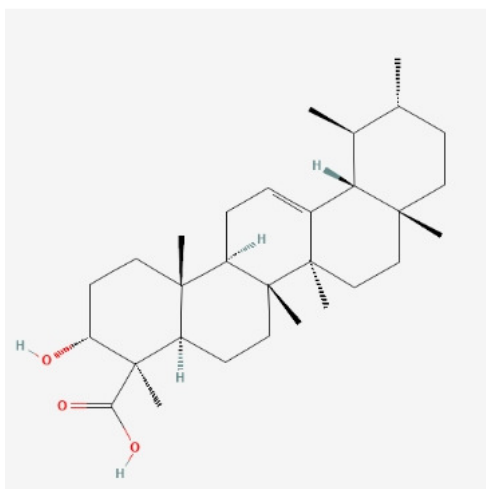
- Functional groups
- Molecular size
- Polarity
- Lipophilicity

Score Range	Interpretation
> 0.00	Active – High probability of interaction with the target class.
–0.50 to 0.00	Moderately Active – Possible interaction; needs further validation.
< –0.50	Inactive – Unlikely to interact significantly with the target.

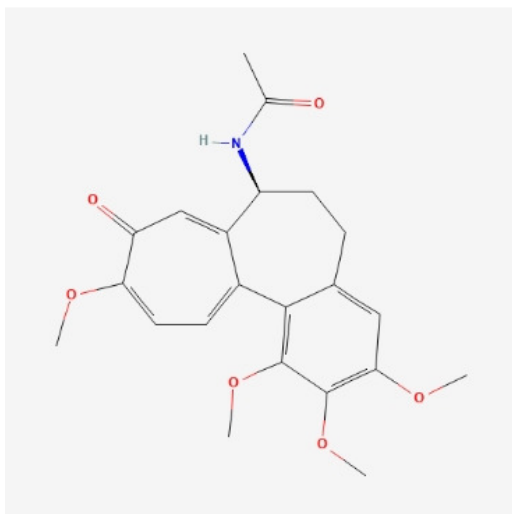
The evaluation studies show that curcumin may show high activity as an enzyme inhibitor and nuclear receptor ligand, supporting its anti-inflammatory role. Colchicine could show broader activity across GPCR, ion channels, and enzyme inhibition. Methotrexate might be strong as an enzyme inhibitor but weak on other targets. Linoleic Acid is likely nutritional rather than pharmacologically active across the predicted targets.¹⁹



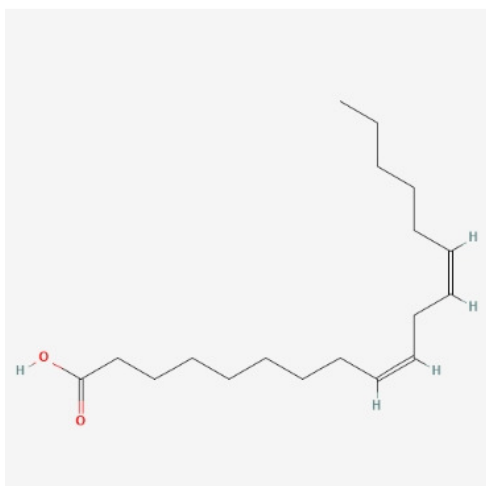
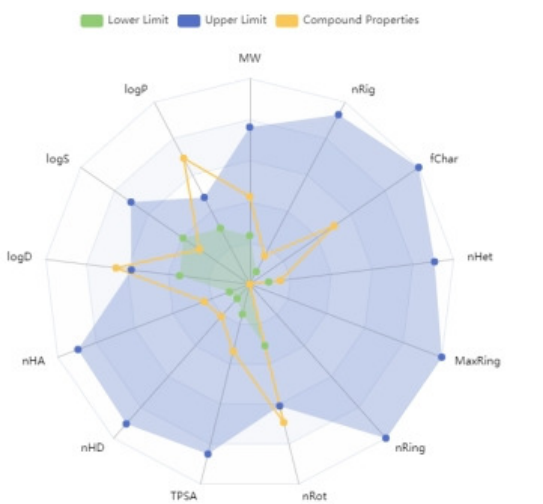
CURCUMIN



BOSWELLIC ACID

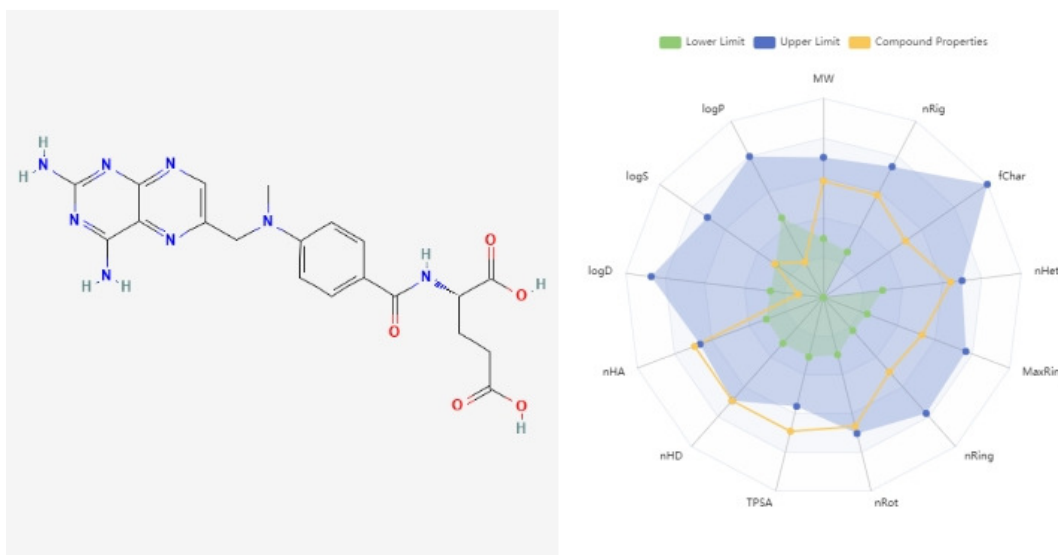


COLCHICINE



LINOLEIC ACID





METHOTREXATE

CONCLUSION

In conclusion, the evaluation of various herbal drugs used to treat Rheumatoid Arthritis was done. The comparison between phytoconstituents of herbal drugs and a marketed synthetic drug was made. We compared parameters like absorption, permeability, distribution, and other factors. However, the research on the exact mechanism of each drug to treat RA is still completely unknown, which needs to be done. From the result, we can see that herbal alternatives like Curcumin may offer a safer profile compared to synthetic drug like Methotrexate in treatment of RA.

The Molinspiration bioactivity predictions validates the therapeutic potential of Curcumin and Boswellic acid as promising enzyme and nuclear receptor modulators. The study supports Colchicine's polypharmacology, particularly relevant to RA's complex inflammatory pathways. It also highlights that Methotrexate, though potent, may have narrower target specificity. Linoleic acid plays a more nutritional and supportive role rather than direct target binding.

References:

- 1] S. K. D. Hewlings, "Curcumin: A Review of Its Effects on Human Health," Foods, vol. 6, no. 10, p. 92, 2017.
- [2] "https://en.wikipedia.org/wiki/Lipinski's_rule_of_five," [Online].

- [3] C. F. B. W. Lipinski, "Experimental and computational approaches to estimate solubility and permeability in drug discovery and development setting," *Advanced Drug Delivery Reviews*, vol. 23, no. 1-3, pp. 3-25, 1997.
- [4] C. A. Lipinski, "Lead and drug-like compounds: The rule-of-five revolution." *Drug Discovery Today: Technologies*, vol. 1, no. 4, pp. 337-341, 2004.
- [5] M. Yang, U. Akbar and C. Mohan, "Curcumin in Autoimmune and Rheumatic Diseases," *Nutrients*, vol. 11, no. 5, 2019.
- [6] B. B. a. B. S. Aggarwal, "Pharmacological basis for the role of curcumin in chronic diseases: An age-old spice with modern targets," *Trends in Pharmacological Sciences*, vol. 30, no. 2, pp. 85-94, 2009.
- [7] S. M.Z, " Boswellia serrata, a potential antiinflammatory agent: an overview.," *Indian Journal of Pharmaceutical Sciences*, vol. 73, no. 3, pp. 255-261, 2011.
- [8] H. B. I. F. Ethan Basch, "Boswellia: An evidence-based systematic review by the Natural Standard Research Collaboration," *Journal of Herbal Pharmacotherapy*, vol. 4, no. 3, pp. 63-83, 2004.
- [9] J. B. D.M. Raditic, "https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/rose-hip," 2014. [Online].
- [10] S. Pekacar, S. Bulut, B. Özüpek and D. D. Orhan, " Anti-Inflammatory and Analgesic Effects of Rosehip in Inflammatory Musculoskeletal Disorders and Its Active Molecules," *Current Molecular Pharmacology*, vol. 14, no. 5, pp. 731-745(15), 2021.
- [11] Pharmacy180," Available: <https://www.pharmacy180.com/article/colchicum-162/>.
- [12] M. B. M. R. K. J. F. B. O. Stanisław Surma, "Colchicine — From rheumatology to the new kid on the block: Coronary syndromes and COVID-19," *Cardiology Journal*, vol. 30, no. 2, pp. 297-311, 2023.
- [13] M. E. Suarez-Almazor, "Methotrexate for treating Rheumatoid Arthritis," *Cochrane Database of Systematic Reviews* , vol. 2014, no. 6, p. CD000957, 2014.
- [14] K. Tripathi, *Essentials of Medical Pharmacology*, New Delhi: Jaypee Brothers Medical Publishers, 8th edition.

[15]Image1:https://media.istockphoto.com/id/171310913/photo/tumericcurcumin.jpg?s=2048x2048&w=is&k=20&c=SnZR7lnGZ4wT5b4f5aSErpEXe7Fh4bbIqYDD1Sju_rI=

[16]Image3:https://media.istockphoto.com/id/1133759143/photo/rosehip.webp?s=2048x2048&w=is&k=20&c=9oeFuWTmr54ATbRAINlPpzFJP5pwvQtyawey_yXOdHs=

[18]Image4;https://media.istockphoto.com/id/1356410507/photo/autumn-crocus-colchicumautumnale.jpg?s=2048x2048&w=is&k=20&c=hPnqMgvNmM_zMHZUX6FrfrfAVKlqaJwVt-8yC9sdkAtI=

19. Molinspiration Cheminformatics Software Website:

<https://www.molinspiration.com>

Tool for molecular property calculation and bioactivity prediction using SMILES input.

Accessed July 2025.