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Research article

IN-SILICO DESIGN AND SCREENING FOR ANTIBACTERIAL ACTIVITY OF SUBSTITUED COUMARIN DERIVATIVES

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Abstract

Background: *The increasing prevalence of antibiotic resistance among pathogenic bacteria has intensified the need for new and effective antibacterial agents. Coumarin derivatives have shown promising antibacterial properties due to their ability to target essential bacterial enzymes such as DNA gyrase B.*

Objective: The study aimed to design and screen novel coumarin derivatives using in-silico methods for potential antibacterial activity against Escherichia coliDNA gyrase B enzyme.

Methods: *A computer-aided drug design (CADD) approach involving structure-based and ligand-based methods was employed. 40 compounds of C3 substitutedcoumarin derivatives were designed and subjected to molecular docking using PyRx 0.8 and interaction analysis with Biovia Discovery Studio. Toxicity profiling was conducted using OSIRIS DataWarrior, and pharmacokinetic properties were evaluated through SwissADME.*

Results and Discussion: *Among the 40 compounds of C3 substituted derivatives, three compounds were determined to be the best analogues after comparing all the criteria.*

Conclusion: *The findings suggest that 3 substituted coumarin derivatives (S20, S21 and S22)have strong potential as lead compounds for the development of novel antibacterial agents targeting DNA gyrase B.*

Keywords: Traditional medicinal practices, West Garo hills, Meghalaya, Ethnomedicinal Documentation, Healthcare

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Introduction

Bacteria are ubiquitous. They are crucial to preserving the surroundings in which we live. The world's bacteria only make up a small portion of those that cause illness and infection [1]. The public's health is greatly impacted by these bacterial diseases. Since there is a larger variety of antimicrobial medicines with effectiveness against bacteria, treating bacterial infections is typically easier than treating viral infections. In contrast to infectious diseases resulting from viruses and parasites, antibiotic resistance in bacteria is an issue that is expanding quickly and has the potential to be extremely harmful. Among the prokaryotes [2,3], bacteria are distinct in that a large number of them are normal flora that colonize the host without infecting it [4].Antimicrobial resistance, according to the World Health Organization, is a natural phenomenon that happens when bacteria become resistant to antibiotics that they were once sensitive to and that were effective in treating infections that these bacteria caused. Drug resistance makes illnesses more difficult or impossible to cure, which raises the possibility of fatalities and the spread of dangerous infectious diseases [5].

Coumarin is a benzopyrone molecule that has a lactone structure and is made up of a fused benzene and α-pyrone ring [6,7]. It is an aromatic molecule with delocalized π-electrons, contributing to its stability and UV absorption. Because of the lactone ring, it can be attacked by nucleophiles and hydrolysed in basic circumstances to produce o-hydroxycinnamic acid. Dihydrocoumarin is created when coumarin undergoes hydrogenation of the pyrone double bond and electrophilic aromatic substitution on the benzene ring. The Pechmann condensation and Perkin reaction, which involve phenols and β-ketoesters or aromatic aldehydes, respectively, are common synthetic pathways [8].

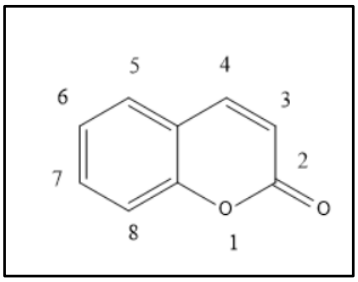


Figure1: Structure of Coumarin

Penta *et al*. stated that Coumarins substituted with 3-ketone, 3-ester and 3-alkoxyimino derivatives were found to be extremely active against gram-positive strain, together with *Staphylococci* and *Enterococcus* species [9].

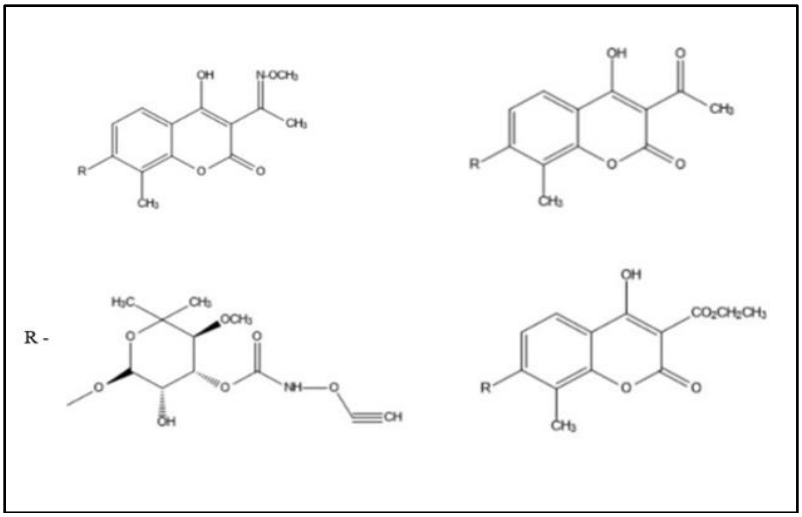


Figure 2: Carbonyl and Alkoxyimine group substitution

The amide compound, substituted with tertiary amine, exhibited helicase inhibitory activity better than the carboxylic group.

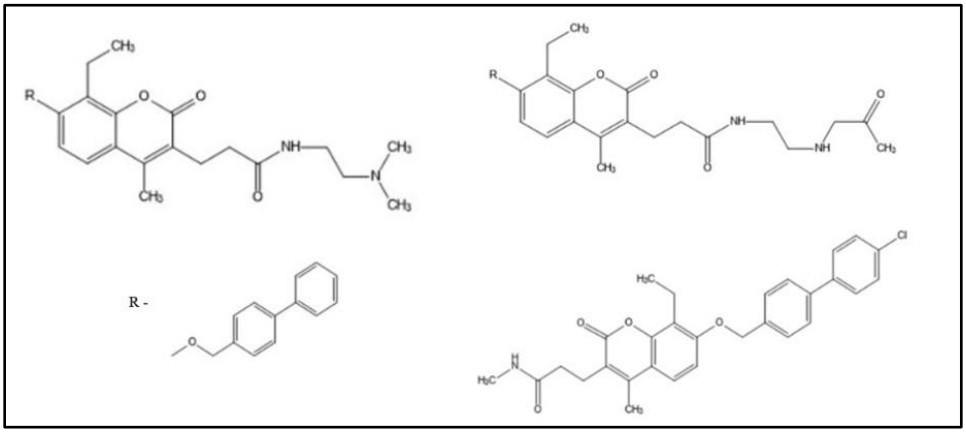


Figure 3: Amide group with alkyl chain substitution

Coumarins substituted with 3-amides, and hydroxamate derivatives shows greatest antibacterial activity, mostly against novobiocin-resistant strains [9].

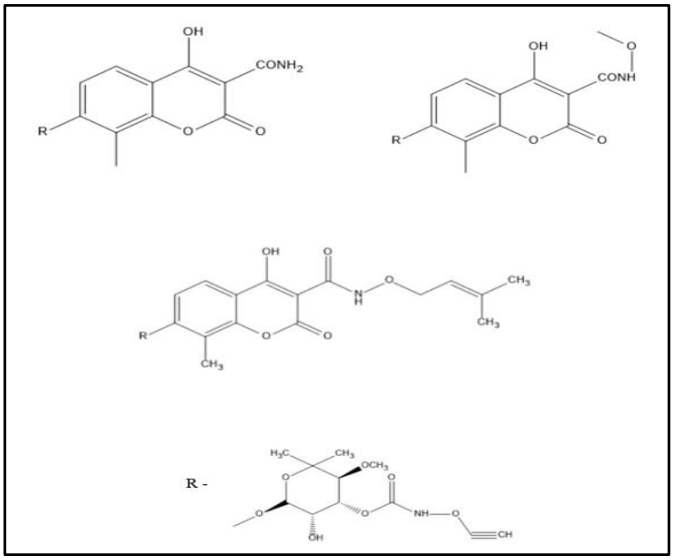


Figure 4: Amide and Hydroxamate group substitution

The hydroxyl group at the 3rd position showed greatest antibacterial activity.

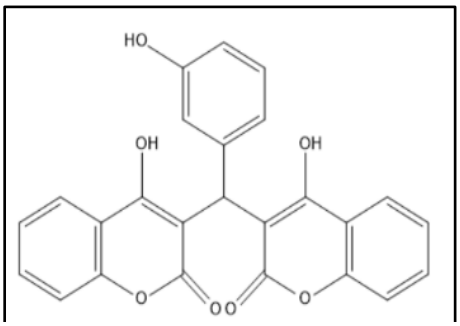


Figure 5: Hydroxyl group substitution

Certain research has revealed that, Coumarin is a DNA Helicase/Gyrase inhibitor i.e. it acts against DNA helicases of some strains of bacteria like *B. anthrasis* and *S. aureus*. DNA helicase produces a replication fork during DNA replication, which unwinds DNA strands and enables the creation of daughter strands from the parental template [7]. DNA helicase inhibitors prevent DNA strands from unwinding, which halts replication. Therefore, bacterial helicase inhibitors can be used to stop the development of bacteria [8].

Materials and Methods:

Retrieval of target protein

According to the MOA of Coumarin, it interacts with the Enzyme "DNA Gyrase B" and stops the unravelling of DNA strands, which stops replication. The protein in

complex with benzothiazole (PDB ID:5L3J)]needed for the docking process was downloaded from Protein Data Bank (RSCB) in PDB format. Antibacterial drug development has confirmed that bacterial DNA gyrase and topoisomerase IV regulate the topological state of DNA during replication [5].

Protein Preparation

The protein is made up of one chain (Chain A) which contains 378 amino acids in its sequence. It is 2.83 Å in resolution. After that, the protein was prepared for docking using BIOVIA DISCOVERY STUDIO. After removing the Ligand and Water molecule, Polar Hydrogens were added and stored in PDB format for further usage [5].

Preparation of Compound Library

For this study, 3 Substituted Coumarin Derivatives were selected as a lead molecule to design some new drug candidates for the inhibition of DNA gyrase B enzyme in bacteria like *Escherichia coli*. A number of its derivatives were created by changing the substituent groups on the 3rd position of the Coumarin ring [10].ChemDraw was used to prepare each of the listed compounds, which were then stored in .sdf format. The 2D structures of 40 compounds for C3 substituted derivatives were drawn using ChemDraw Pro 12.0.2.1076 and saved in .sdf format. The SMILES (Simplified Molecular Input Line Entry System) of all the compounds drawn were also obtained and saved as data in MS-Excel [11].

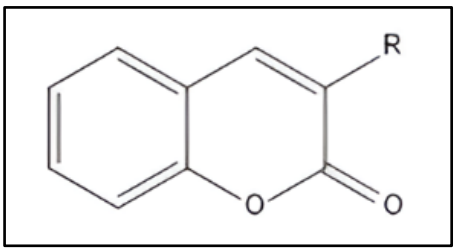


Figure6: 3-Substituted Coumarin Derivative

Energy minimization of ligands

Utilizing the PyRx 0.8 program, the ligands' energy was minimized. The PyRx 0.8 virtual screening tool's default parameters were used to minimize the ligands.

Molecular docking simulation studies

After the protein was ready, it was loaded into PyRx 0.8. It was then transformed into a macromolecule by right-clicking on the protein and selecting "Autodock". The compounds were then all converted to the .pdbqt format.The initial target protein complexed with 6G9 was loaded using the PyRx virtual screening platform. The chain composed of proteins complexed with 6G9 was shown by enlarging the protein and the amino acid chains in the raw protein became visible [11,12]. After labelling the Native Ligand, or 6G9, the 3D affinity grid box was meticulously

constructed to align with the core region of 6G9, covering all of the residues in the active site while taking into account the active binding site and the location of the 6G9 on the protein. The original protein was then eliminated from the area.

Visualization and analysis of ligand interactions

After accessing BIOVIA Discovery Studio 2021, prepared protein was loaded. Analogues were loaded to interact with the prepared protein, which was defined as a receptor [13]. A two-dimensional diagram that represented their interaction was seen and saved for upcoming usage. For each of the other derivatives, the procedure was repeated. After eliminating the analogues that failed to exhibit conventional hydrogen bonding, the remaining ones were tested for toxicity.

Toxicological Studies

To ascertain a substance's safety, toxicity testing is performed. It helps us determine whether a molecule or substance is detrimental to an organism's normal biological function. 'OSIRIS Datawarrior' was utilized for this process [14]. All created derivatives' SMILES CODE were uploaded into the Data Warrior, and each derivative was tested for Mutagenicity, Tumorigenicity, Reproductive Effect, And Skin Irritation. The toxic compounds were eliminated, and the remaining compounds were examined further for ADME studies.

ADME Studies

SwissADME was used to conduct ADME studies. The ADME properties of the substances that remained after toxicity studies are examined. The SMILE Codes of the remaining chemicals are assessed based on their Lipinski Rule of 5 after being uploaded to SwissADME.

Results and Discussion

Features of the target protein

The crystal structure of chain A of *E. coli* DNA Gyrase B was retrieved from the RCSB-PDB website [15]. The protein is comprised of multiple chains, among which chain A was selected for further analysis and docking. The structure (PDB ID: 5L3J) is complexed with a co-crystallized inhibitor,namely 2-((2-(4,5-dibromo-1H-pyrrole-2-carboxamido) benzothiazol-6-yl) amino)-2-oxoacetic acid, a potent DNA gyrase B inhibitor. This ligand is a derivative of the benzothiazole class and functions by occupying the ATP-binding pocket of the enzyme, thereby blocking DNA supercoiling activity essential for bacterial replication [16]. It was used as a reference compound wherever necessary in the present study. This compound belongs to the broader class of 4,5,6,7-tetrahydrobenzo[1,2-d]thiazole-based scaffolds, which have shown strong nanomolar inhibition against *Staphylococcus aureus* and *Escherichia coli* DNA gyrase and topoisomerase IV [17,18].

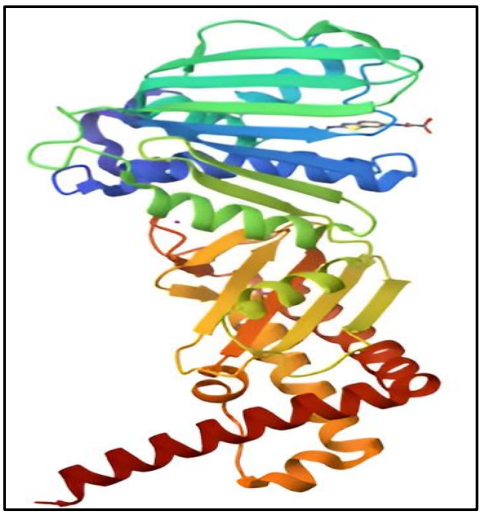
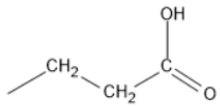
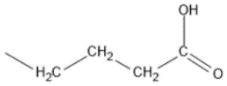
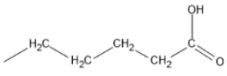
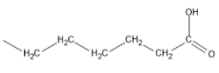
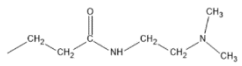
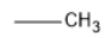
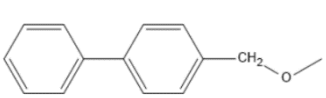
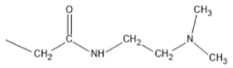
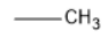
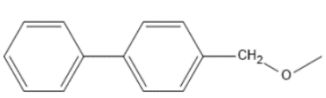
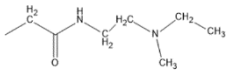
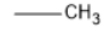
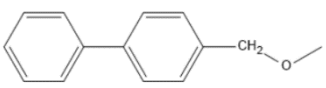
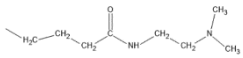
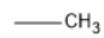
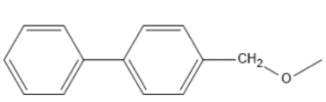
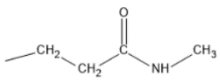
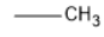
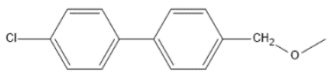
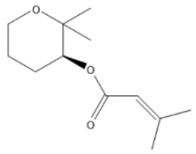
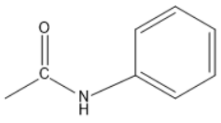
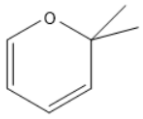
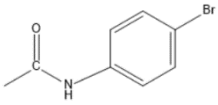
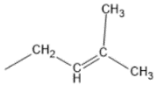
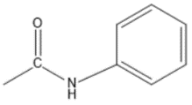


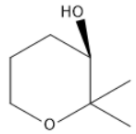
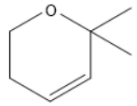
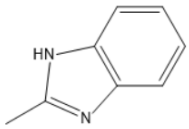
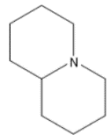
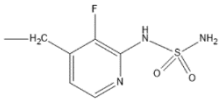
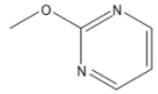
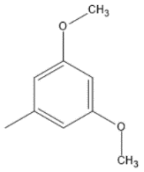
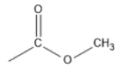
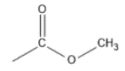
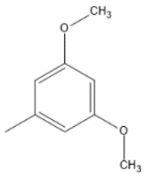
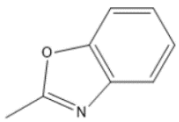
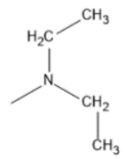
Figure 7: *Escherichia coli* DNA Gyrase B Protein (PDB ID: 5L3J) [5]

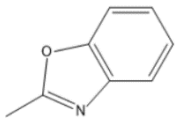
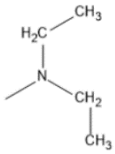
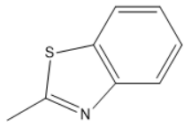
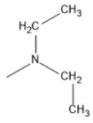
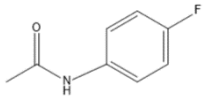
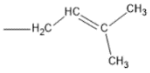
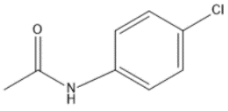
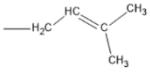
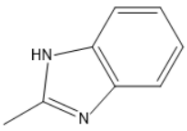
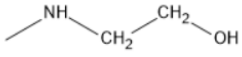
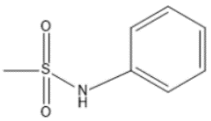
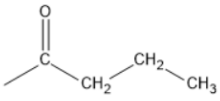
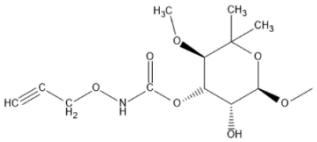
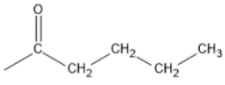
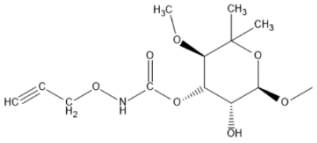
Structures of Derivatives

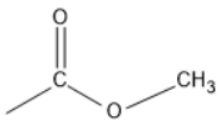
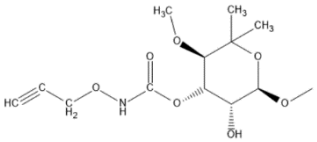
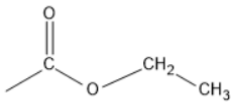
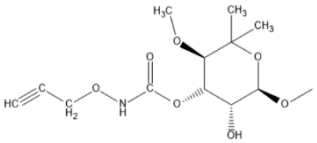
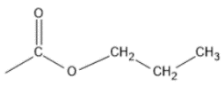
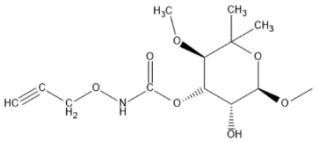
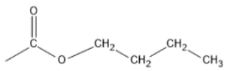
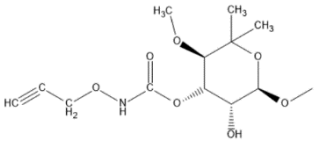
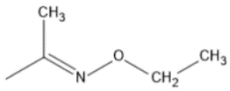
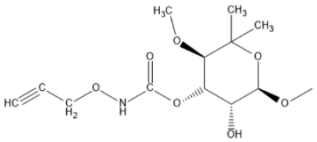
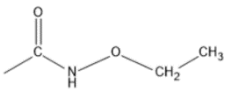
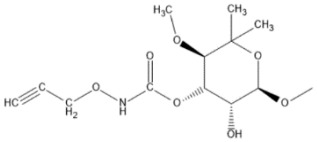
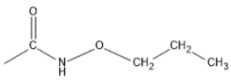
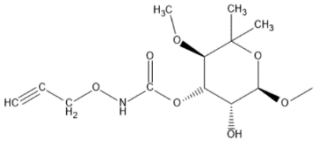
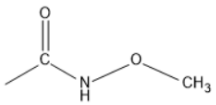
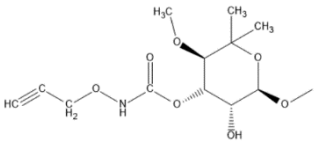
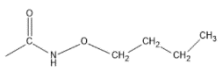
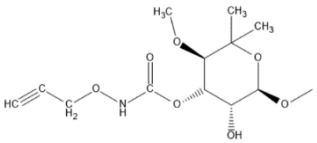
Table 1: Structure of 3-Substituted Coumarin Derivatives

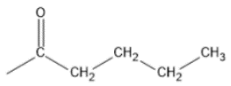
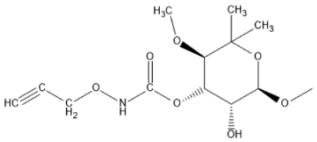
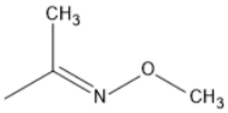
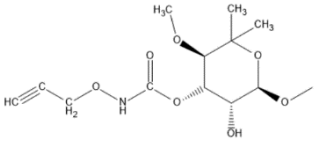
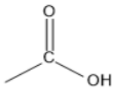
Compd Code	R3	R4	R6	R7	R8
S1			-		
S2			-		
S3			-		
S4			-		

S5			-		
S6			-		
S7			-		
S8			-		
S9			-		
S10	-	-			-
S11		-			-
S12		-			-
S13		-	-	-	-

S14	-	-		-
S15	-	-		-
S16		-		
S17		-		-
S18		-		
S19		-		
S20		-		-

S21		-	-		-
S22		-	-		-
S23		-		—OH	-
S24		-		—OH	-
S25		-	-		-
S26		-	-	-	-
S27		—OH	-		—CH_3
S28		—OH	-		—CH_3

S29		—OH	-		—CH_3
S30		—OH	-		—CH_3
S31		—OH	-		—CH_3
S32		—OH	-		—CH_3
S33		—OH	-		—CH_3
S34		—OH	-		—CH_3
S35		—OH	-		—CH_3
S36		—OH	-		—CH_3
S37		—OH	-		—CH_3

S38		—OH	-		—CH_3
S39		—OH	-		—CH_3
S40		-	-	-	-

Molecular docking simulation studies

A computational method called molecular docking forecasts potential interactions between a medication and a protein [19]. It provides insight into a drug's ability to inhibit a protein implicated in a disease network. In order to rank the binding potential of ligands towards a protein [20], MDSS is performed on PyRx software, which yields a binding affinity value (-kcal/mol) for each ligand.

Table 2: Binding Affinity of 3-Substituted Coumarin Derivatives

Serial No.	**Compound Code**	**Binding Affinity (-kcal/mol)**
1.	**Native Ligand**	**-7.3**
2.	S1	-8.9
3.	S2	-8.7
4.	S3	-8.8
5.	S4	-8.4
6.	S5	-8.1
7.	S6	-8.0
8.	S7	-8.3
9.	S8	-7.7
10.	S9	-8.8
11.	S10	-8.2
12.	S11	-8.7

13.	S12	-8.8
14.	S13	-7.9
15.	S14	-8.0
16.	S15	-8.0
17.	S16	-9.8
18.	S17	-7.8
19.	S18	-7.4
20.	S19	-7.8
21.	**S20**	**-8.5**
22.	**S21**	**-9.4**
23.	**S22**	**-9.6**
24.	S23	-8.5
25.	S24	-8.8
26.	S25	-8.5
27.	S26	-7.7
28.	S27	-7.2
29.	S28	-7.1
30.	S29	-6.8
31.	S30	-7.2
32.	S31	-6.6
33.	S32	-7.4
34.	S33	-7.2
35.	S34	-7.1
36.	S35	-7.2
37.	S36	-7.1
38.	S37	-7.0
39.	S38	-7.2
40.	S39	-7.2
41.	S40	-7.3

After comparing the Binding affinities of all the derivatives with the Binding Affinity of Native Ligand, it was found that the binding affinity of 25 compounds werebetter than the binding energy of Native Ligand [21,22]. The selected compounds are S1, S2, S3, S4, S5, S6, S7, S8, S9, S10, S11, S12, S13, S14, S15, S16, S17, S18, S19, S20, S21, S22, S24, S26 and S40.
Therefore, the Interactions of the compounds with the prepared protein was studied.

Visualization and analysis of ligand interactions

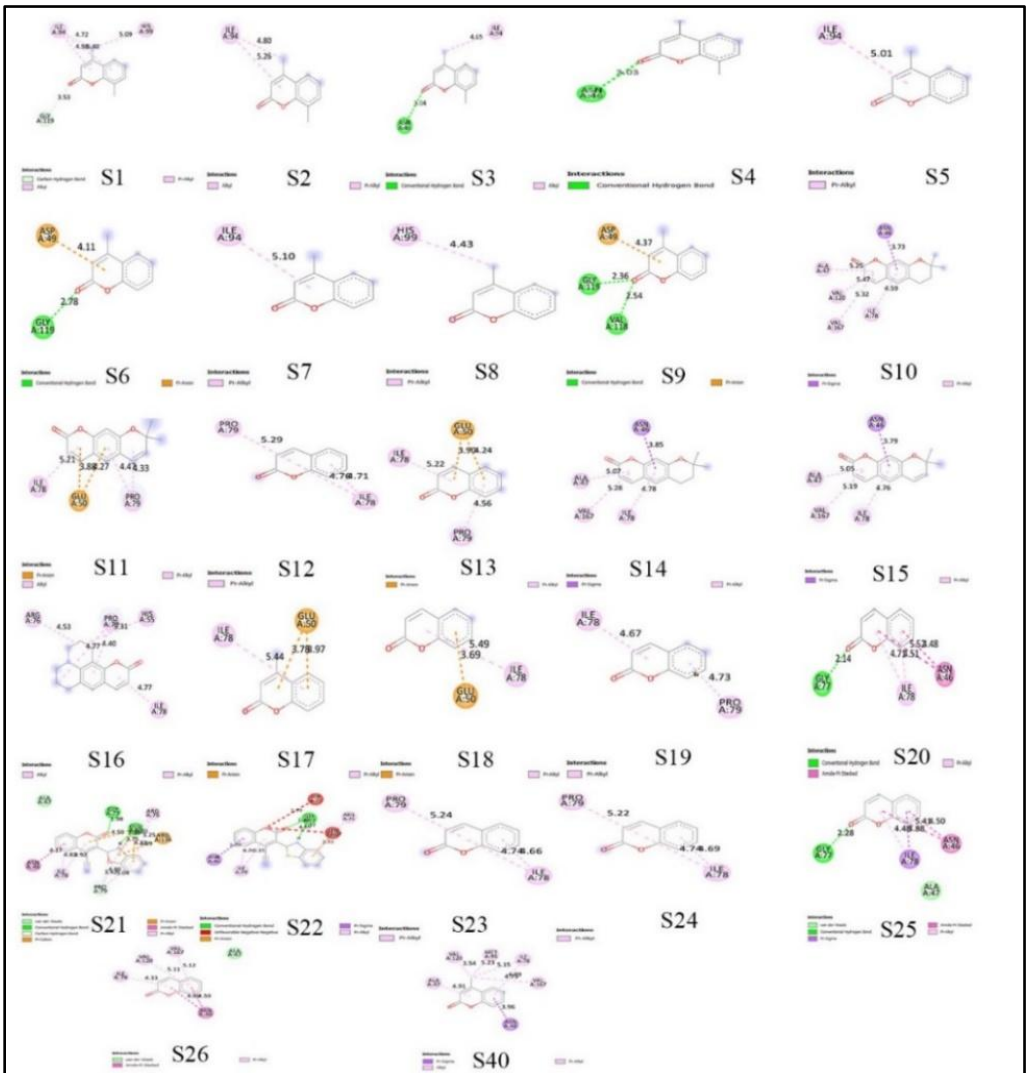


Figure 8: Ligand Receptor Interaction

Table 3: Ligand-Receptor Interaction of 3-Substituted Coumarin Derivatives

Serial No.	Compd Code	Conventional H-Bonding	Others
1.	Native Ligand	-	ILE78 (3.70 Å), ASN46 (3.94 Å)
2.	S1	-	ILE94 (4.72 Å), (4.98 Å), (5.40 Å), HIS99 (5.09 Å), GLY119 (3.53 Å)
3.	S2	-	ILE94 (4.80 Å), (5.26 Å)
4.	S3	ASN46 (3.04 Å)	ILE94 (4.65 Å)
5.	S4	ASN46 (3.03 Å)	-
6.	S5	-	ILE94 (5.01 Å)
7.	S6	GLY119 (2.78 Å)	ASP49 (4.11 Å)
8.	S7	-	ILE94 (5.10 Å)
9.	S8	-	HIS99 (4.43 Å)
10.	S9	GLY119 (2.36 Å) VAL118 (2.54 Å)	ASP49 (4.37 Å)
11.	S10	-	ASN46 (3.73 Å), ILE78 (4.59 Å), VAL167 (5.32 Å), VAL120 (5.47 Å), ALA47 (5.25 Å)
12.	S11	-	ILE78 (5.21 Å), GLU50 (3.88 Å), (4.27 Å), PRO79 (4.47 Å), (4.33 Å)
13.	S12	-	PRO79 (5.29 Å) ILE78 (4.76 Å), (4.71 Å)
14.	S13	-	GLU50 (3.90 Å), (4.24 Å), PRO79 (4.56 Å), ILE78 (5.22 Å)
15.	S14	-	ASN46 (3.85 Å), ILE78 (4.78 Å),

			VAL167 (5.28 Å), ALA47 (5.07 Å)
16.	S15	-	ALA47 (5.05 Å), VAL167 (5.19 Å), ILE78 (4.76 Å), ASN46 (3.79 Å)
17.	S16	-	ARG76 (4.53 Å), PRO79 (4.77 Å), (4.40 Å), HIS55 (5.31 Å), ILE78 (4.77 Å)
18.	S17	-	LE78 (5.44 Å), GLU50 (3.78 Å), (3.97 Å)
19.	S18	-	GLU50 (3.69 Å), ILE78 (5.49 Å)
20.	S19	-	ILE78 (4.67 Å), PRO79 (4.73 Å)
21.	**S20**	**GLY77 (2.15Å)**	**ILE78 (4.71Å), (4.51Å), ASN46 (5.52Å), (4.48Å)**
22.	**S21**	**GLY77 (1.98Å) GLU50 (2.16Å)**	**ASN46 (4.17Å), ILE78 (4.83Å), (4.92 Å), PRO79 (3.42 Å), (5.04 Å), (4.80 Å), GLU50 (4.50 Å), (4.32 Å), (3.75 Å), ALA47, ARG136 (4.99 Å), ARG76 (5.25 Å), (5.20 Å)**
23.	**S22**	**GLY77 (2.28Å), (2.17Å)**	**ASN46 (3.99 Å), ILE78 (4.76Å), (5.15Å), ASP73 (3.99Å), GLU50 (4.65Å), (3.93Å), ARG76 (5.07Å)**
24.	S24	-	PRO79 (5.22Å), ILE78 (4.74Å), (4.69Å)
25.	S26	-	ILE78 (4.33 Å), ASN46 (4.69 Å), (4.59 Å), VAL120 (5.11 Å), VAL167 (5.12 Å), ALA47
26.	S40	-	VAL120 (3.54 Å), MET95 (5.23 Å), ILE78 (5.15 Å), (4.89 Å), VAL167 (4.73 Å), ASN46 (3.96 Å), ALA47 (4.91 Å)

From Table 3, it was found that out of 25 Compounds, compounds S1, S2, S3, S4, S5, S6, S7, S8, S9, S10, S11, S12, S13, S14, S15, S16, S17, S18, S19, S24, S26 and S40, didn't showed any kind of Conventional H-bonding. Therefore, we can eliminate these compounds and the remaining compounds are further taken for toxicity analysis [23].

Toxicity Studies

The remaining 7 compounds after eliminating compounds S1, S2, S3, S4, S5, S6, S7, S8, S9, S10, S11, S12, S13, S14, S15, S16, S17, S18, S19, S24, S26 and S40 are analyzed for their toxicity using **'OSIRIS Datawarrior'.**

Table 4: Toxicity Analysis of 3-Substituted Coumarin Derivatives

Serial No.	Compound code	Mutagenicity	Tumorigenic	Reproductive	Irritant
1.	S3	None	None	High	High
2.	S4	None	None	High	High
3.	S6	None	None	High	High
4.	S9	None	None	High	High
5.	**S20**	**None**	**None**	**None**	**None**
6.	**S21**	**None**	**None**	**None**	**None**
7.	**S22**	**None**	**None**	**None**	**None**

From the toxicity analysis data, it was found that out of 7 compounds, only compound S20, S21 and S22 are found Non-Toxic [24]. Therefore, all the other compounds except compounds S20, S21 and S22 are eliminated and the non-toxic compounds are analyzed further for ADME studies.

ADME Studies: The compounds S20, S21 and S22 are analyzed for their ADME properties using SwissADME. The Smile Codes for compounds S20, S21 and S22 are uploaded and studied if they followed Lipinski's rule [25].

Table 5: ADME Results of 3-Substituted Coumarin Derivatives

Serial Number	Compound Code	Molecular Weight (g/mol)	H-bond Acceptor	H-bond Donor	iLOGP (o/w)	Lipinski Violation
1.	**S20**	**334.37**	**4**	**0**	**5.32**	**0 violation**
2.	**S21**	**359.38**	**5**	**0**	**3.32**	**0 violation**
3.	**S22**	**375.44**	**4**	**0**	**3.35**	**0 violation**

The compounds S20, S21 and S22 were found to comply with the Lipinski rule of 5 and since they do not violate any rules, they can be selected for further studies.

Conclusion

Here, we identified a few candidates that exhibited increased *in-silico* activity. Compounds S20, S21 and S22 were determined to be the best analogues after comparing all the criteria, such as binding energy, ADME attributes, toxicity data and ligand-protein interactions. This was because of their strong binding affinity with protein (5L3J), absence of toxicity, and good ADME features. These analogues can be created and examined *in vitro* in the future to verify the antibacterial efficacy shown in this in-silico study.

Declarations

Conflict of interest

The authors declare no conflicting interest.

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Author's contributions

SS carried out the study on C3-substituted derivatives. SS also carried out the drafting of the manuscript and prepared it according to the journal guidelines. MS guided the entire research process, including compound selection, data analysis, and manuscript development. DC supervised the study, critically reviewed the manuscript, and provided additional scientific input. All authors read and approved the final manuscript.

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Research article

STUDY ON TRADITIONAL MEDICINAL PRACTICES FOLLOWED IN WEST GARO HILLS OF MEGHALAYA

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Abstract

Background*: Meghalaya is rich in floral diversity, with medicinal and aromatic plants accounting for a considerable portion. The natural resources of Meghalaya's Garo Hills are abundant not only in terms of flora and fauna but also in traditional medicinal practices.*

Objective: *To study and document systematically the traditional medicinal practices followed in selected areas of West Garo hills of Meghalaya.*

Methods: *The information on traditional medicinal practices was collected from traditional healers by using questionnaire in a standard format prepared by the authors.. The study was carried out by interviewing traditional healers and village elders of village Dadenggre, Baljek Songgitcham, west Garo Hills (Meghalaya). They were interviewed and their treatment details were recorded in the information sheets.*

Results and Discussion*:The study culminated in successfully documenting various traditional medicinal practices particularly in the different areas of Dadenggrelocated in West Garo hills of Meghalaya.*

Conclusion: *The information provided in the project is limited and there is always a scope to initiate more ethnobotanical study among the ethnic communities of West Garo Hills of Meghalaya to gather information as far as possible. The findings of the present study proves that the people have immense faith on the effectiveness of their herbal medicines. In the backdrop of the rapidly changing socio-cultural and economic changes it is high time to document their ethnomedical knowledge and make the people aware about the increasing importance as well as the global scenario of ethnomedicine.*

Keywords: Traditional medicinal practices, West Garo hills, Meghalaya, Ethnomedicinal Documentation, Healthcare

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Introduction

Human beings by nature depend on Mother Nature. From time immemorial, people have been gathering knowledge about the nature and the environment. The knowledge thus gathered from long observations and experiences becomes an inevitable part of human society and life. The congregate knowledge base is then passed on from one generation to the next, which at later periods or at present are known as traditional knowledge [1]. The knowledge of medicinal plants and its conservation is found among all the tribal communities of India. Plants have served mankind since ages as they are reservoirs of important medicinal components and help to alleviate chronic diseases.

However, for a long time such traditional knowledge were unexplored, undocumented and without proper protection. Currently, unauthorized use and the misappropriation of medicinal plants have stimulated the need for scientific exploration and documentation of traditional systems of medicine. Currently, much attention is being paid to the significance of traditional herbal medicine in public health in both developed and developing countries. According to World Health Organization (WHO), nearly 80% of the world population rely on the use of traditional medicines to meet their primary health care need [2] .Traditional medicine include all kinds of folk medicine, unconventional medicine and indeed any kind of therapeutic method that had been handed down by the tradition of a community or ethnic group. The medical traditions in the traditional system are diverse in their historical background, theoretical logic and practices, their contemporary social realities and their dynamics [3].

Traditional healing is one of the oldest method of treatment which is based upon underlying philosophy as well as set of principles by which it is being practiced. It is the medicine from which all later forms of medicine are developed, including Chinese medicine, Graeco-Arabic medicine and of course also modern Western medicine. Traditional healing practice was an integral part of Semi-nomadic and agricultural tribal societies, the archeological evidence for its existence dates back to around 6000 BC [4,5].

There were still some regional differences between the principles and philosophy of traditional healing although there are many fundamental similarities that arise from the profound knowledge of natural laws and the understanding of how these influence traditional medical practitioner or traditional healers well defined as one who is recognized by the community in which he lives as competent to provide health care by using vegetable, animal, and mineral substances, as well as certain other methods based on the social, cultural, and religious backgrounds, as well as prevailing knowledge of physical, mental, and social health"[6]

Prospects of Northeast India

Northeast (NE) India is the homeland of a large number of tribes. The NE regions comprising of Assam, Arunachal Pradesh, Manipur, Meghalaya, Mizoram, Nagaland, Sikkim and Tripura is inhabited with large number of tribal's of various ethnic group. They depend on the surrounding plant resources which form an integral part of their traditional health care system. It has a valuable heritage of herbal medicines. Its rural people and tribal living in remote/forest areas still depend to a great extent on the indigenous systems of medicine and cultivation. North East states of India are highly riched in medicinal and aromatic plants. Due to its unique and variance in topography and climatic condition, this region has high medicinal plant diversity. Studies of folk medicines and practices through ethnomedicinal survey gained a specific importance in the region and the numerous cultivated and wild plants also plays a very important role among culture [7].

Meghalaya is rich in floral diversity, with medicinal and aromatic plants accounting for a considerable portion of the total, and the state has a long history of medical plant use. The growth of the medicinal plants sector in Meghalaya has a lot of potential for creating jobs because there is a big and growing market for medicinal and aromatic plants and their preparations. The natural resources of Meghalaya's Garo Hills are abundant. Forests, minerals, and water resources are the most important natural resources on which the state's economy is heavily reliant. Forests

provide the most to the state's economy of all natural resources. Garo Hills woods offer a wide range of floral diversity due to the varied climatic and geographical circumstances [8,9].

Materials and Methods

An Ethnomedicinal survey was conducted in selected areas of West Garo Hills of Meghalaya (Figure 1) to study and document systematically the traditional medicinal practices followed in selected areas of West Garo hills of Meghalaya. The selected study areas include Bolchugri Gittim, Aʾjigri gittim, Modil gittim, Gadarugre and Aʾsim Achura.

The information on traditional medicinal practices was collected from traditional healers by using questionnaire in a standard format prepared by the authors. The study was carried out by interviewing traditional healers and village elders of village Dadenggre, Baljek Songgitcham, West Garo Hills (Meghalaya). They were interviewed and their treatment details were recorded in the prepared information sheets. First-hand information about the local names of different ethno medicinal plants, their formulation, uses, and doses against the particular disease were recorded.

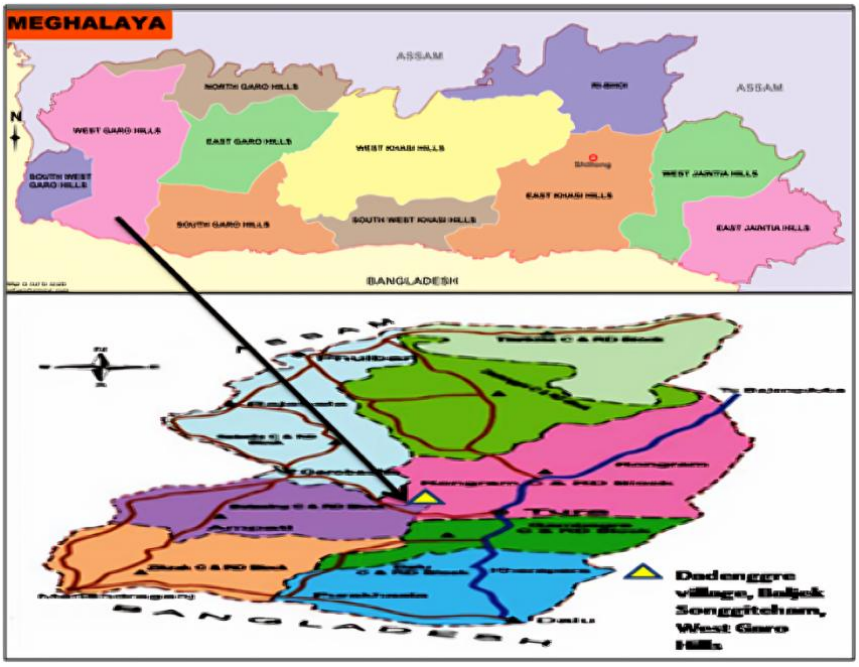

Figure 1: Map representing the location of an area of study

Results and Discussion

The information compiled during the study period are summarized in tabular form in Table 1 to Table 14. Table 2 to Table 7 contains the data about the Medicinal plants and its Formulation used to treat Hypertension, Kidney stone, Oligomenorrhea(Irregular Periods),Urinary Tract Infection(UTI),Jaundice and Myositis, Sprain and contusion given by local healer of Bolchugri gittim, A'jigri gittim and Modil gittim area of Baljek Songgitcham village. Table9-table 14 contains the information about the Medicinal plants and its Formulation used to treat Ringworm, Blood clotting, During Snake bite, Malaria, Giddiness and for Purifying Blood & Wound healing collected from the local healer of Gadarugre, Dadenggre and Aʾsim Achura.The details of information collected from the local traditional healer (Ojha) of Baljek Songgitcham village(Table 1) during the survey are represented in Table 2 to Table 7.

Table 1: Details of the local traditional healer of Baljek Songgitcham village

Local Medicinal Practitioner details	
Name	Walenson A Sangma
Age	88 years
Gender	Male
Survey area	Bolchugri gittim, A'jigri gittim and Modil gittim
Village	Baljek Songgitcham
District	West Garo hills
Occupation	Traditional healer (ojha)

Table 2:Medicinal plants & formulation used to treat hypertension

Plant Name (local):- Dongam bijak	Scientific name: - *Clerodendrum glandulosum* Lindl (Verbenaceae)
Plant type:- perennial shrub	Plant part used:- Leaf
Locality from where collected by local healers:- Bolchugri gittim	
Other plants and materials used for preparation of medication(if any):- Matcha duri (*Houttuynia cordata*) and Tebrong bijak (*Artocarpus heterophyllus*)	
Additives and vehicle used for medication:- Water	
Formulation prescribed as:- Advice to take b.i.d for 20-30 days (orally)	
Method of Processing and preparation:- -2-3 fresh leaves from the above mentioned medicinal plants were collected and washed - Then grinded to make a fine paste - 1 spoonful from the prepared paste was mixed with hot water in a tea cup and make up to 50% of its total volume - Then it is filtered with a cotton cloth and administered orally	
Other uses if any of the plant(s):- Treatment of cough,diabetes,rheumatism	

Figure 2: Photograph of Dongam bijak (*Clerodendrum glandulosum* L.) found in Bolchugri gittim area

Table 3: Medicinal plants & formulation used to treat Kidney Stone

Plant Name (local):- Patorchira	Scientific name: - *Kalanchoe pinnata* (Crassulaceae)
Plant type:- Succulent shrub	Plant part used:- Leaf
Locality from where collected by local healers:- A'jigri gittim	
Other plants and materials used for preparation of medication(if any):- - Memang Katchi (*Achyranthes aspera*) - Sammikchip (*Mimosa pudica*) - Neem (*Azadirachta indica*)	
Additives and vehicle used for medication:- Water	
Formulation prescribed as:- Advice to take b.i.d for 2-3 months (orally)	
Method of Processing and preparation:-	

- Fresh leaves(3-4) of above mentioned plants were grinded and made into a fine paste
- ½ teaspoon of the paste was poured in a cup of hot water
- Then equal amount of hot water was added
- Then it is filtered with a cotton cloth and administered orally at regular intervals

Other uses if any of the plant(s):- Psychiatric disorders, prevent premature labour

Figure 3: Photograph of Patorchira (*Kalanchoe pinnata*) found in A'jigri gittim area

Table 4: Medicinal plants & formulation used to treat Oligomenorrhea

Plant Name (local):- Sojina	Scientific name: - *Moringa oleifera* (Moringaceae)
Plant type:- Small deciduous tree	Plant part used:- Leaf
Locality from where collected by local healers:- Modil gittim	
Other plants and materials used for preparation of medication(if any):- - Sammikchip (*Mimosa pudica*) -Joba Bibal(*Hibiscus rosa-sinensis*)	
Additives and vehicle used for medication:- Water	
Formulation prescribed as:- Advice to take t.i.d (Orally)	
Method of Processing and preparation:- - Fresh leaves(5-6) of above mentioned plants were grinded and made into a fine paste - Then the paste was boiled in water for 10-12 minutes - Then it is filtered with a cotton cloth and administered orally	
Other uses if any of the plant(s):- Antioxidant & Anti-inflammatory effects, reduce blood cholesterol	

Figure 4: Photograph of Sojina (*Moringa oleifera*) found in Modil gittim area

Table 5: Formulation & medicinal plants used to treat Urinary Tract Infection (UTI)

Plant Name (local):- Samsureng	Scientific name: - *Clerodendrum serratum*(Lamiaceae)
Plant type:- Shrub	Plant part used:- Leaf
Locality from where collected by local healers:- A'jigri gittim	
Other plants and materials used for preparation of medication(if any):- - Memang ambari(*Phyllanthus amarus*) - Gokarek (*Cheilocostus speciosus*)	
Additives and vehicle used for medication:- Water	
Formulation prescribed as:- Advice to take t.i.d (Orally)	

Method of Processing and preparation:-
- 3-4 leaves of above mentioned plants were grinded to make a fine paste
- Then the paste was mixed with water and stirred vigorously for 7-8 minutes
- Then it is filtered with a cotton cloth and administered orally
Other uses if any of the plant(s):- Antiseptic,astringent,styptic, asthma & cough

Figure 5: Photograph of Samsureng (*Clerodendrum serratum***)** found in A'jigri gittim area

Table 6: Formulation & medicinal plants used to treat Jaundice

Plant Name (local):- Memang Katchi	Scientific name: - *Achyranthes aspera* (Amaranthaceae)
Plant type:- Herb	Plant part used:- Leaf
Locality from where collected by local healers:- Modil gittim	
Other plants and materials used for preparation of medication(if any):-	

- Prap Bijak (*Ficus benghalensis*)
- Memang ambari(*Phyllanthus amarus*)
- Kering Bijak (*Oroxylum indicum*)
- Koronda(*Ricinus communis*)
- Aski pul (*Catharanthus roseus*)

Additives or vehicle used for medication:- Water

Formulation prescribed as:- Advice to take t.i.d for one week (orally)

Method of Processing and preparation:-

- After collecting the fresh leaves of above mentioned plants, a fine paste was made by grinding
- About ½ spoon of the prepared paste was boiled in water for 10-15 minutes.
- Then it is filtered with a cotton cloth and administered orally

Other uses if any of the plant(s):- cough,rheumatism,malaria,diabetes

Figure 6: Photograph of Memang Katchi (*Achyranthes aspera*) found in Modil gittim area

Table 7: Formulation & medicinal plants used to treat Myositis, Sprain and contusion

Plant Name (local):- Do'ja gipe	Scientific name: - *Justicia gendarussa* (Acanthaceae)
Plant type:- Shrub	Plant part used:- Leaf
Locality from where collected by local healers:- Bolchugri gittim	
Other plants and materials used for preparation of medication(if any):- - Rajamoli (*Crinum asiaticum*)	
Additives and vehicle used for medication:- No (Banana leaves are used for wrapping while burning in charcoal)	
Formulation prescribed as:- Advice to applied b.i.d (Topically)	
Method of Processing and preparation:- - 2-3 fresh leaves of above mentioned plants were collected and washed - Its then wrapped in banana leaves and heated in charcoal fire under medium heat - The heated wrapped bundle was slowly massaged over the fractured or swollen part - The process is continued until pain relief	
Other uses if any of the plant(s):- Jaundice,cephalgia,eczema	

Figure 7: Photograph of Do'ja gipe (*Justicia gendarussa*) found in Bolchugri gittim area

The details of information collected from the local traditional healer of Gadarugre, Dadenggre and Aʾsim Achura village (Table 8) during the survey are represented in Table 9 to Table 15.

Table 8: Details of the local traditional healer of Gadarugre, Dadenggre and Aʾsim Achura village

Local Medicinal Practitioner details	
Name	Remilla A Sangma
Age	76 years
Gender	Female

Survey area	Gadarugre, Dadenggre and Aʾsim Achura
Village	Baljek Songgitcham
District	West Garo hills
Occupation	Traditional healer (ojha)

Table 9: Medicinal plants used to treat Ringworm

Plant Name (local):- Memang Koksi	Scientific name: - *Nepenthes khasiana* (Nepenthaceae)
Plant type:- Small perennial herb	Plant part used:- Leaf
Locality from where collected by local healers:- Gadarugre,Dadenggre	
Other plants and materials used for preparation of medication(if any):- No	
Additives and vehicle used for medication:- No	
Formulation prescribed as:- Apply once in a day until proper recovery (topically)	
Method of Processing and preparation:- - 3-4 leaves of above mentioned plants were collected and grinded to make a fine paste - Paste is applied in the affected area after proper cleaning - Patients will be cautioned for burning sensation after application of the paste - This procedure is done once daily until recovery	
Other uses if any of the plant(s):- Digestive disorder, diabetes	

Figure 8: Photograph of Memang Koksi (*Nepenthes khasiana*) found in Gadarugre and Dadenggre area

Table 10: Medicinal plants used as Anticoagulant

Plant Name (local):- Wakme budu	Scientific name: - *Mucuna pruriens* (Fabaceae)
Plant type:- Annual climbing shrub	Plant part used:- Stem
Locality from where collected by local healers:- A'sim Achura	
Other plants and materials used for preparation of medication(if any):- No	
Additives and vehicle used for medication:- No	
Formulation prescribed as:- Advice to apply the prepared liquid immediately after injury	

Method of Processing and preparation:-

-The stem of matured plant of *Mucuna pruriens* were collected and washed properly

- Stem juice is squeeze out the using mechanical pressure

- Then juice is applied in the injured/cut part to prevent blood clot

Other uses if any of the plant(s):- Male infertility, nervous disorders, as an aphrodisiac

Figure 9: Photograph of Wakme budu (*Mucuna pruriens*) found in A'sim Achura area

Table 11: Medicinal plants used for Snake bite

Plant Name (local):- Dikgi bisi	Scientific name: - *Curcuma zedoaria* (Zingiberaceae)
Plant type:- Perennial herb	Plant part used:- Rhizome
Locality from where collected by local healers:- Gadarugre,Dadenggre	
Other plants and materials used for preparation of medication(if any):- No	
Additives and vehicle used for medication:- Water	
Formulation prescribed as:- Fresh extract of rhizome taken orally or rhizome paste can be applied over bitten area for 1-2 days or until relief (for immediate result)	
Method of Processing and preparation:- - A fine paste from the collected rhizome part of the above mentioned plant was made - The prepared paste was mixed with a proper amount of water and administered orally - For emergency purpose, the prepared rhizome paste is applied over the bitten area and tied with a cloth	
Other uses if any of the plant(s):- Digestive problem and for purifying blood	

Figure 10: Photograph of Dikgi bisi (*Curcuma zedoaria*) found in Gadarugre and Dadenggre area

Table 12: Medicinal plants used to treat Malaria

Plant Name (local):- Do-Grikmi	Scientific name: - *Rauvolfia serpentina* (Apocynaceae)
Plant type:- herb	Plant part used:- root
Locality from where collected by local healers:- A'sim Achura	
Other plants and materials used for preparation of medication(if any):- - Chirota (*Swertia chirata*) - Samkiljeng (*Artemisia verlotiorum*)	
Additives and vehicle used for medication:- Few food taboos are used while taking	

the medicines like pork, jack fruit, Mesing leaves, Chuka leaves etc.

Formulation prescribed as:- Advice to take with food taboos (banana,tamarind,mesing leaves etc.) during malarial season

Method of Processing and preparation:-

- Plants are harvested in August and collected in September.
- They are then dried in the autumn sun, which aids in the plants rapid dehydration.
- Dried plants are gathered and stored in a tightly sealed container.
- The powdered medications are maintained in a well-sealed container and protected from direct sunlight.
- When taking medicines, there are several food taboos to consider, such as pork, bananas, jackfruit, Mesing leaves, and Chuka plants.

Other uses if any of the plant(s):- arthritis, high blood pressure, mental disorders

Figure 11: Photograph of Do-Grikmi (*Rauvolfia Serpentina*) found in A'sim Achura area

Table 13: Medicinal plants used to treat Giddiness

Plant Name (local):- Achetra gitchak	Scientific name: - *Alternanthera brasiliana* (Amaranthaceae)
Plant type:- perennial herb	Plant part used:- Leaf
Locality from where collected by local healers:- A'sim Achura	
Other plants and materials used for preparation of medication(if any):- No	
Additives and vehicle used for medication:- No	

Formulation prescribed as:- Advice to applied topically over head
Method of Processing and preparation:- - 3-4 leaves of above mentioned plant was collected and grinded into a fine paste - After that the prepared paste was applied over the head (Mainly scalp part) by packing with a fine cloth - This activity was repeated until complete recovery
Other uses if any of the plant(s):- Inflammation,analgesic,wound healing

Figure 12: Photograph of Achetra gitchak (*Alternanthera brasiliana*) found in A'sim Achura area

Table 14: Medicinal plants used for Purifying Blood & Wound healing

Plant Name (local):- Walmagul	Scientific name: - *Alternanthera bettzickiana* (Amaranthaceae)
Plant type:- perennial herb	Plant part used:- Leaf
Locality from where collected by local healers:- Gadarugre,Dadenggre	
Other plants and materials used for preparation of medication(if any):- No	
Additives and vehicle used for medication:- No	
Formulation prescribed as:- Advice to applied topically over wound area & take the extract orally for purifying blood	
Method of Processing and preparation:- - 2-3 fresh leaves of above mentioned plants were collected and washed - Then grinded up all the leaves and made into a fine paste - Paste was mixed in a cup of water and given orally blood purification - In case of wound, the prepared paste was applied and kept for 1 hour.	
Other uses if any of the plant(s):- treatment of anemia in children, antipyretic agent, Laxative	

Figure 13: Photograph of Walmagul (*Alternanthera bettzickiana*) found in Gadarugre and Dadenggre area

Conclusion

Medicinal Plants continue to play an important role for the people of Garo Hills, Meghalaya. Therefore, it is extremely essential to conserve the medicinal plants and the indigenous knowledge of Garo tribe. West Garo Hills is one of the largest district of Meghalaya located in the western part of the State which is considered as one of the biodiversity hotspot of northeast in its potential as traditional medicinal practices and hub of various medicinal plants.

A field study of traditionally used medicinal plant around the periphery of west Garo Hills has been conducted to explore the ethnobotanical uses of varied plants with their pharmacological effect. After the study it's revealed that this region has immense potential in medicinal plants of various therapeutic values. Keeping in climatic diversities of the locality, it's observed that the standard and quantitative phytoconstituents serves important information about the local plants.

During the study different areas of Dadenggre and other villages were visited. The knowledge that local healers of West Garo Hills used for plants gives a transparent idea about the crude botanical preparation of medicinal plants. The study was successful in documenting various plants and there formulations pertaining to blood purification, Wound healing, Malaria, Snake bite, Anticoagulant, Antihelmintic, Sprain, Jaundice, UTI, Oligomenorrhea, Kidney Stone & Hypertension.

Conflict of Interest: None

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Research article

TRADITIONAL KNOWLEDGE AND THERAPEUTIC PRACTICES OF THE POUMAI NAGA TRIBE OF KOIDE VILLAGE, MANIPUR

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Abstract

Background: *Koide village, located in the Senapati district of Manipur, India, is home to the Lepaona group of the Poumai Naga tribe. The region, characterized by dense forests and terraced farming, is rich in biodiversity and traditional knowledge of medicinal plants. This study documents the ethnobotanical practices of the Poumai Naga tribe, focusing on their use of indigenous flora for therapeutic purposes.*

Objective: *The study aimed to document the traditional knowledge of medicinal plants in Koide village, including their therapeutic applications, preparation methods, and socio-cultural significance.*

Methods: An ethnographic approach was employed, with primary data collected through in-depth interviews with Mr. Souba Thaio, a traditional healer, and field visits to collect plant specimens. Interviews focused on identifying medicinal plants, their uses, and preparation methods, supported by local guides and botanical references.

Results and Discussion: *The study documented 14 medicinal plants used for various ailments, including Clereodendrum glandulosum (diabetes, hypertension), Sambucus chinensis (body pain), Chromolaena odorata (wound healing), Curcuma augustifolia (cough, fever), and Rhododendron arboreum (bone obstruction). Preparation methods ranged from boiling leaves for decoctions to applying plant juices directly to affected areas. The findings highlight the rich ethnobotanical knowledge of the Poumai Naga tribe, emphasizing the socio-cultural and therapeutic significance of these plants. The study underscores the urgent need to preserve this knowledge, which is at risk due to modernization. The documented plants hold potential for pharmacological research and development of herbal medicines.*

Conclusion: *This study provides valuable insights into the traditional medicinal practices of Koide village, emphasizing the importance of conserving both biodiversity and indigenous knowledge. Further scientific validation of these plants could integrate traditional practices into modern healthcare, ensuring their sustainable use for future generations.*

Keywords: Medicinal plant, Manipur, Poumai Naga tribe, Ethnobotanical knowledge.

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Introduction

The use of plants in medicine dates back thousands of years, rooted in the trial-and-error exploration of their diverse applications, ranging from food to ritualistic practices. Over time, this empirical knowledge evolved into more systematic and scientific investigations of the medicinal properties of plants. Despite the dominance of modern medicine and pharmaceutical advancements in contemporary healthcare, plants have remained a cornerstone of medicinal practices worldwide. From ancient herbal traditions to modern pharmacological research, the therapeutic potential of plants continues to play a vital role in addressing human health concerns. Many of today's widely used pharmaceuticals, such as aspirin, trace their origins to traditional herbal remedies. Aspirin, for instance, was derived from the bark of the willow tree, which has been used for centuries to alleviate pain and reduce fever [1]. This enduring connection between plants and medicine underscores the importance of exploring and preserving traditional knowledge of medicinal flora.

The northeastern region of India, particularly the state of Manipur, is renowned for its rich biodiversity and deep-rooted traditional knowledge systems. Manipur, often referred to as the "Land of Gems," is a unique state characterized by its diverse topography, temperate climate, and vibrant cultural heritage [2]. Nestled in the northeastern part of India, it is bordered by Nagaland to the north, Assam to the west, Mizoram to the southwest, and Myanmar to the south and east. The state's capital, Imphal, lies in the central valley, which experiences a temperate climate with distinct seasonal variations. The surrounding hills, cooler in comparison, contribute to the region's ecological diversity. Manipur's economy is primarily driven by agriculture, forestry, and traditional cottage industries, supported by its abundant natural resources. With a population that has grown from 2.29 million in 2001 to 2.85 million in 2011, Manipur continues to evolve while maintaining its rich cultural and ecological identity[3].

Within Manipur, the Senapati district, particularly the village of Koide, stands out for its ecological and cultural richness. This region is home to a wealth of indigenous flora, many species of which possess significant medicinal and therapeutic properties. The local communities in Koide have preserved and passed down traditional knowledge about the use of these plants for generations, relying on them to treat various ailments like blood pressure,wound healing, piles,cough, fever etc. This harmonious relationship between the community and its natural environment highlights the importance of documenting and conserving such indigenous knowledge systems, which are increasingly threatened by modernization and environmental degradation [4].

This study focuses on the therapeutic potential of the indigenous flora of Koide village, Senapati district, aiming to bridge the gap between traditional knowledge

and contemporary pharmacological research. By documenting the traditional uses of these plants this research seeks to underscore the relevance of these plants in the context of sustainable healthcare. Furthermore, the study emphasizes the importance of preserving the rich biodiversity and cultural heritage of Koide village, ensuring that this invaluable knowledge is celebrated and conserved for future generations. Through this work, we aspire to contribute to the sustainable utilization of medicinal plants, fostering a deeper appreciation for the intricate relationship between humans and their natural environment.

Materials and Methods

Study Area

The study was conducted in Koide village, located in the Senapati district of Manipur, India. Senapati district is situated in the northern part of Manipur and is bordered by Ukhrul District to the east, Tamenglong District to the west, Phek District of Nagaland to the north, and Imphal East and Imphal West to the south. The district is characterized by its picturesque landscape, comprising blue hills, lush valleys, and winding rivers. It spans an area of 3,271 square kilometers and lies at an altitude ranging from 1,061 to 1,788 meters above sea level. The climate in Senapati varies from 34.14°C in summer to 3.36°C in winter, with the rainy season extending from June to September. Approximately 80% of the district is covered in dense forests, while the remaining 20% is utilized for agriculture, primarily terraced farming of crops such as rice, maize, cabbage, and potatoes.

Koide village, nestled amidst the lush green hills of Senapati, is home to the Lepaona group of the Poumai Naga tribe. The village is divided into Upper and Lower Koide and is one of the 84 Poumai revenue-recognized villages. The Poumai Naga tribe, with a population of 1,79,189 as per the 2011 census, has a rich cultural heritage and a deep connection to the natural environment. Koide village is approximately 39.8 kilometers from Senapati town and about 12–15 kilometers from Lairouching, another village in the district. The village is known for its rich biodiversity and traditional knowledge of medicinal plants, which have been preserved and passed down through generations.

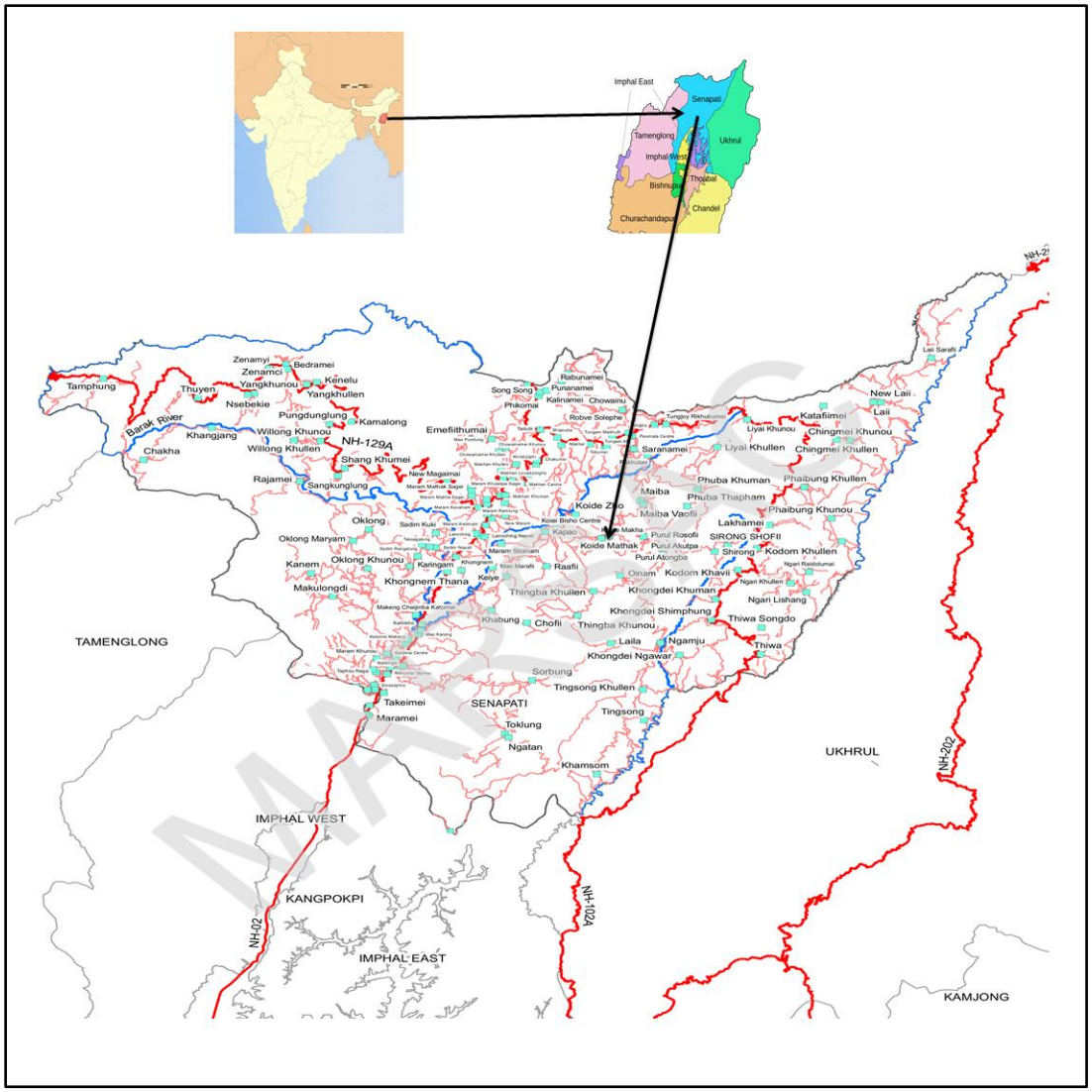

Figure 1: Map representing the location of area of study; Koide Village, Senapati, Manipur.

Data Collection

The study employed an ethnographic approach to document the traditional knowledge of medicinal plants in Koide village. Primary data were collected through in-depth interviews and discussions with Mr. Souba Thaio, a renowned traditional healer from Koide village. Mr. Thaio, born on October 10, 1950, has extensive knowledge of the therapeutic uses of indigenous flora, which he acquired from his elders during his childhood. His expertise in traditional healing, coupled

with his dedication to preserving the cultural heritage of the Poumai Naga tribe, made him a key informant for this study.

The interviews were conducted in the local language and focused on identifying the medicinal plants used by the community, their traditional applications, and the methods of preparation and administration. Information was also gathered on the socio-cultural significance of these plants and their role in the daily lives of the villagers.

Figure 2: Mr. Souba Thaio, traditional healer from Koide village.

Ethical Considerations

Prior informed consent was obtained from Mr. Souba Thaio and the village community before conducting the study. The research adhered to ethical guidelines for the documentation of traditional knowledge, ensuring that the intellectual property rights of the community were respected. The study also aimed to contribute to the preservation and sustainable utilization of the region's medicinal plants, aligning with the community's interests and values.

Data Analysis

The collected data were systematically documented to identify the medicinal plants and their traditional uses. The socio-cultural significance of these plants were also analysed to understand their role in the community's healthcare practices and cultural heritage.

Limitations

The study acknowledges certain limitations, including the reliance on a single key informant for traditional knowledge, which may not capture the full diversity of

medicinal plant use in the region. Additionally, the study focused primarily on qualitative data, and further research involving phytochemical and pharmacological analyses is recommended to validate the therapeutic potential of the documented plants.

Results and Discussion

Table 1: Details of the local traditional healer of Koide village.

Local Medicinal Practitioner details	
Name	Mr. Souba Thaio
Age	74yrs.
Gender	Male
Survey area	Koide Mathak, Koide Makha, Purul, Koide Zho, Biisho,
Village	Koide village
District	Senapati
Occupation	Traditional healer

Figure 3: Photograph of Nouvuh (*Clereodendrum glandulosm*) found in Koide Zho Village, Senapati, Manipur.

Table 2: Traditional medicinal plant documentation table of Nouvuh (*Clereodendrum glandulosm)*.

Category	Details
1. Plant Identification	
- Local Name	Nouvuh, East Indian glory bower, Nephaphu
- Scientific Name	*Clereodendrum glandulosm* Family: *Lamiacea*
- Plant Type	Shrub
2.Traditional Uses	Traditionally used to treat diabetes, hypertension, cough, and rheumatism in ethnomedicine for its therapeutic properties.
3. Plant Part Used	
- Specific Part(s) Used	Leaves
- Condition of Use	Fresh
4. Collection Details	
- Locality	Koide Zho Village, Senapati, Manipur.
- Season/Time of Collection	13th October, 2024
- Collector	Mr. Souba Thaio & Ms. H. Vaveinai
5. Preparation & Formulation	
- Other Plants or Materials Used (If any)	No
- Additives or Vehicles	Water
- Formulation Type	Decoction, Extract
6. Processing & Administration	
- Method of Processing	Boiling
- Dosage & Frequency	Twice daily
- Mode of Administration	Oral
7. Other Traditional Uses	
- Additional Ethnobotanical Uses	Food
- Known Side Effects (If any)	Low blood pressure

Figure 4: Photograph of Rahbo (*Sambucus chinensis*) found in Koide mathak village, Senapati, Manipur.

Table 3: Traditional medicinal plant documentation table of Rahbo (*Sambucus chinensis*).

Category	Details
1. Plant Identification	
- Local Name	Rahbo, Chinese Elder,

- Scientific Name	*Sambucus chinensis* Family: *Adoxaceae*
- Plant Type	Shrub
2.Traditional Uses	Traditionally used to alleviate body pain resulting from trauma, such as physical injuries, accidents, or falls.
3. Plant Part Used	
- Specific Part(s) Used	Leaves
- Condition of Use	Fresh
4. Collection Details	
- Locality	Koide mathak village, Senapati, Manipur.
- Season/Time of Collection	11th October, 2024
- Collector	Mr. Souba Thaio & Ms. H. Vaveinai
5. Preparation & Formulation	
- Other Plants or Materials Used (If any)	No
- Additives or Vehicles	Water
- Formulation Type	Infusion
6. Processing & Administration	
- Method of Processing	Steeping
- Dosage & Frequency	Twice daily
- Mode of Administration	Topical
7. Other Traditional Uses	
- Additional Ethnobotanical Uses	No
- Known Side Effects (If any)	Nausea, vomiting

Figure 5: Photograph of Nuodai (*Leucas ciliata*) found in Koide mathak village, Senapati, Manipur.

Table 4: Traditional medicinal plant documentation table Nuodai (*Leucas ciliata*).

Category	Details
1. Plant Identification	
- Local Name	Nuodai, Tufted Leucas, Burumbi, Tshangla,
- Scientific Name	*Leucas ciliata* Family: *Lamiaceae*
- Plant Type	Herb
2.Traditional Uses	Traditionally employed for managing sinus-related conditions, including inflammation and congestion, due to its therapeutic properties.

3. Plant Part Used	
- Specific Part(s) Used	Leaves
- Condition of Use	Fresh
4. Collection Details	
- Locality	Koide Mathak Village, Senapati, Manipur.
- Season/Time of Collection	10th October, 2024
- Collector	Mr. Souba Thaio & Ms. H. Vaveinai
5. Preparation & Formulation	
- Other Plants or Materials Used (If any)	No
- Additives or Vehicles	No
- Formulation Type	Extract
6. Processing & Administration	
- Method of Processing	Crushing
- Dosage & Frequency	2 drops twice daily
- Mode of Administration	Inhalation
7. Other Traditional Uses	
- Additional Ethnobotanical Uses	Food
- Known Side Effects (If any)	Dizziness

Figure 6: Photograph of Pou moh/ Pou hou moh (*Chromolaena odorata)* found in Koide Makha Village, Senapati, Manipur.

Table 5: Traditional medicinal plant documentation table of Pou moh/ Pou hou moh (*Chromolaena odorata).*

Category	Details
1. Plant Identification	
- Local Name	Pou moh/ Pou hou moh, Devil weed, Siam weed, Christmus Bush, Camphor grass, Communist weed, etc.
- Scientific Name	*Chromolaena odorata* Family: *Asteraceae*
- Plant Type (Herb/Shrub/Tree/Climber)	Shrub
2.Traditional Uses	Traditionally utilized for wound healing (haemostasis), and as an antimicrobial agent to prevent infections and promote recovery.
3. Plant Part Used	
- Specific Part(s) Used	Leaves
- Condition of Use	Fresh

4. Collection Details	
- Locality	Koide Makha Village, Senapati, Manipur.
- Season/Time of Collection	10^{th} October, 2024
- Collector	Mr. Souba Thaio & Ms. H. Vaveinai
5. Preparation & Formulation	
- Other Plants or Materials Used (If any)	No
- Additives or Vehicles	No
- Formulation Type	Extract
6. Processing & Administration	
- Method of Processing	Crushing & Squeezing
- Dosage & Frequency	Once daily
- Mode of Administration	Topical
7. Other Traditional Uses	
- Additional Ethnobotanical Uses	No
- Known Side Effects (If any)	Not known

Figure 7: Photograph of Paopou (*Laggera crispata*) found in Koide Makha Village, Senapati, Manipur.

Table 6: Traditional medicinal plant documentation table of Paopou (*Laggera crispata*).

Category	Details
1. Plant Identification	
- Local Name	Paopou, Curly Blumea
- Scientific Name	*Laggera crispata* Family: *Asteraceae*
- Plant Type (Herb/Shrub/Tree/Climber)	Herb
2.Traditional Uses	Traditionally used to treat piles, cough, fever, gastrointestinal disorders, and eye pain due to its therapeutic properties.
3. Plant Part Used	
- Specific Part(s) Used	Leaves

- Condition of Use	Fresh
4. Collection Details	
- Locality	Koide Makha Village, Senapati, Manipur.
- Season/Time of Collection	10th October, 2024
- Collector	Mr. Souba Thaio & Ms. H. Vaveinai
5. Preparation & Formulation	
- Other Plants or Materials Used (If any)	No
- Additives or Vehicles	No
- Formulation Type	Decoction
6. Processing & Administration	
- Method of Processing	Boiling- For fever Heating- for Eye pain
- Dosage & Frequency	Twice daily
- Mode of Administration	Oral, Topical
7. Other Traditional Uses	
- Additional Ethnobotanical Uses	No
- Known Side Effects (If any)	Not known

Figure 8: Photograph of Hea/Hea muh pou (*Sigesbeckia orientalis*) found in Koide Makha Village, Senapati, Manipur.

Table 7: Traditional medicinal plant documentation table of Hea/Hea muh pou (*Sigesbeckia orientalis*).

Category	Details
1. Plant Identification	
- Local Name	Hea/Hea muh pou, Indian weed/common St.Paul's wort
- Scientific Name	*Sigesbeckia orientalis* Family: *Asteraceae*
- Plant Type	Shrub
2. Traditional Uses	Traditionally employed in the

	management of diarrhoea and dysentery for its potential antidiarrheal and antimicrobial properties.
3. Plant Part Used	
- Specific Part(s) Used	Leaves
- Condition of Use	Fresh
4. Collection Details	
- Locality	Koide Makha Village, Senapati, Manipur.
- Season/Time of Collection	10^{th} October, 2024
- Collector	Mr. Souba Thaio & Ms. H. Vaveinai
5. Preparation & Formulation	
- Other Plants or Materials Used (If any)	No
- Additives or Vehicles	No
- Formulation Type	Extract
6. Processing & Administration	
- Method of Processing	Crushing & Squeezing
- Dosage & Frequency	10-20ml daily
- Mode of Administration	Oral
7. Other Traditional Uses	
- Additional Ethnobotanical Uses	No
- Known Side Effects (If any)	Not known

Figure 9: Photograph of Boh Lasiihou (*Brugmansia suaveolens*) found in Koide Mathak Village, Senapati, Manipur.

Table 8: Traditional medicinal plant documentation table of Boh Lasiihou (*Brugmansia suaveolens*).

Category	Details
1. Plant Identification	
- Local Name	Boh Lasiihou, Angel`s trumpet
- Scientific Name	*Brugmansia suaveolens* Family: *Solonaceae*
- Plant Type	Shrub
2. Traditional Uses	Traditionally utilized as an antidote for venomous bites from snakes, dogs, cats, or other poisonous animals due to its detoxifying properties.

3. Plant Part Used	
- Specific Part(s) Used	Bark
- Condition of Use	Fresh
4. Collection Details	
- Locality	Koide Mathak Village, Senapati, Manipur.
- Season/Time of Collection	10th October, 2024
- Collector	Mr. Souba Thaio & Ms. H. Vaveinai
5. Preparation & Formulation	
- Other Plants or Materials Used (If any)	No
- Additives or Vehicles	No
- Formulation Type	NA
6. Processing & Administration	
- Method of Processing	Peeling
- Dosage & Frequency	Once daily
- Mode of Administration	Topical
7. Other Traditional Uses	
- Additional Ethnobotanical Uses	No
- Known Side Effects (If any)	Dizziness, Nausea

Figure 10: Photograph of Koutu Pah (*curcuma augustifolia*) found in Koide Makha Village, Senapati, Manipur.

Table 9: Traditional medicinal plant documentation table of Koutu Pah (*curcuma augustifolia*).

Category	Details
1. Plant Identification	
- Local Name	Koutu pah, East Indian arrowroot, narrow-leaved turmeric
- Scientific Name	*Curcuma augustifolia* Family: *Zingiberaceae*
- Plant Type	Herb
2.Traditional Uses	Traditionally used to alleviate symptoms of cough and fever due to its potential antipyretic and antitussive properties.
3. Plant Part Used	
- Specific Part(s) Used	Roots

- Condition of Use	Fresh
4. Collection Details	
- Locality	Koide Makha Village, Senapati, Manipur.
- Season/Time of Collection	10th October, 2024
- Collector	Mr. Souba Thaio & Ms. H. Vaveinai
5. Preparation & Formulation	
- Other Plants or Materials Used (If any)	No
- Additives or Vehicles	Water
- Formulation Type	Decoction
6. Processing & Administration	
- Method of Processing	Boiling
- Dosage & Frequency	Thrice daily
- Mode of Administration	Oral
7. Other Traditional Uses	
- Additional Ethnobotanical Uses	Food
- Known Side Effects (If any)	Not known

Figure 11: Photograph of Veihvu (*Spilanthes acmella*) found in Koide Mathak Village, Senapati, Manipur.

Table 10: Traditional medicinal plant documentation table of Veihvu (*Spilanthes acmella*).

Category	Details
1. Plant Identification	
- Local Name	Veihvu, Toothache plant, buzz button, tingflower, electric daisy etc...
- Scientific Name	*Spilanthes acmella* Family: *Asteracea*
- Plant Type	Herb
2.Traditional Uses	Traditionally employed for relieving toothache due to its analgesic and anti-inflammatory properties.
3. Plant Part Used	
- Specific Part(s) Used	Leaves, Flowers
- Condition of Use	Fresh
4. Collection Details	

- Locality	Koide Mathak Village, Senapati, Manipur.
- Season/Time of Collection	10th October, 2024
- Collector	Mr. Souba Thaio & Ms. H. Vaveinai
5. Preparation & Formulation	
- Other Plants or Materials Used (If any)	No
- Additives or Vehicles	No
- Formulation Type	
6. Processing & Administration	
- Method of Processing	Chewing/Crunching
- Dosage & Frequency	Thrice daily
- Mode of Administration	Topical
7. Other Traditional Uses	
- Additional Ethnobotanical Uses	No
- Known Side Effects (If any)	Allergies (To some people)

Figure 12: Photograph of Pao Thaio Poupah (*Ageratum conyzoides*) found in Koide Mathak Village, Senapati, Manipur.

Table 11: Traditional medicinal plant documentation table of Pao Thaio Poupah (*Ageratum conyzoides*).

Category	Details
1. Plant Identification	
- Local Name	Pao Thaio poupah, Billygoat weed, Chick wood, Goatwood or Whiteweed
- Scientific Name	*Ageratum conyzoides* Family: *Asteraceae*
- Plant Type	Herb
2.Traditional Uses	Traditionally used for wound healing, pain relief, and treating abscesses due to its anti-inflammatory, analgesic, and antimicrobial properties.

3. Plant Part Used	
- Specific Part(s) Used	Leaves
- Condition of Use	Fresh
4. Collection Details	
- Locality	Koide Mathak Village
- Season/Time of Collection	19th October, 2024
- Collector	Mr. Souba Thaio & Ms. H. Vaveinai
5. Preparation & Formulation	
- Other Plants or Materials Used (If any)	No
- Additives or Vehicles	No
- Formulation Type	Extract
6. Processing & Administration	
- Method of Processing	Crushing & squeezing
- Dosage & Frequency	Once daily
- Mode of Administration	Topical
7. Other Traditional Uses	
- Additional Ethnobotanical Uses	No
- Known Side Effects (If any)	Not Known

Figure 13: Photograph of Pii Pii Hou (*Drymaria cordata*) found in Koide Mathak Village, Senapati, Manipur.

Table 12: Traditional medicinal plant documentation table of Pii Pii Hou (*Drymaria cordata*).

Category	Details
1. Plant Identification	
- Local Name	Pii pii hou, West Indian chickweed, Tropical chickweed, Stangries or Golondrina
- Scientific Name	*Drymaria cordata* Family: *Caryophyllaceae*
- Plant Type	Herb
2.Traditional Uses	Traditionally utilized for managing fever due to its potential antipyretic and therapeutic properties.
3. Plant Part Used	
- Specific Part(s) Used	Leaves, Roots, Flowers,
- Condition of Use	Fresh
4. Collection Details	
- Locality	Koide Mathak Village, Senapati, Manipur.

- Season/Time of Collection	19th October, 2024
- Collector	Mr. Souba Thaio & Ms. H. Vaveinai
5. Preparation & Formulation	
- Other Plants or Materials Used (If any)	No
- Additives or Vehicles	Water
- Formulation Type	Decoction, Extract
6. Processing & Administration	
- Method of Processing	Boiling, Crushing& Squeezing
- Dosage & Frequency	5ml daily
- Mode of Administration	Oral, Topical
7. Other Traditional Uses	
- Additional Ethnobotanical Uses	No
- Known Side Effects (If any)	Weakness

Figure 14: Photograph of Ha Huh Dao La (*Eleusine indica*) found in Koide Mathak Village, Senapati, Manipur.

Table 13: Traditional medicinal plant documentation table of Ha Huh Dao La (*Eleusine indica*).

Category	Details
1. Plant Identification	
- Local Name	Ha huh dao la, Indian goosegrass, Yardgrass, Goosegrass, Wiregrass, or Crowfootgrass
- Scientific Name	*Eleusine indica* Family: Poaceae
- Plant Type	Herb
2.Traditional Uses	Traditionally employed to alleviate menstrual pain and cramps due to its analgesic and antispasmodic properties.
3. Plant Part Used	
- Specific Part(s) Used	Leaves, Roots,
- Condition of Use	Fresh
4. Collection Details	
- Locality	Koide Mathak Village, Senapati, Manipur.
- Season/Time of Collection	11th 0ctober, 2024
- Collector	Mr. Souba Thaio & Ms. H. Vaveinai
5. Preparation & Formulation	
- Other Plants or Materials Used (If any)	No
- Additives or Vehicles	Water
- Formulation Type	Decoction
6. Processing & Administration	
- Method of Processing	Boiling,
- Dosage & Frequency	Twice daily
- Mode of Administration	Oral
7. Other Traditional Uses	
- Additional Ethnobotanical Uses	No
- Known Side Effects (If any)	Not known

Figure 15: Photograph of Khii Tou Lou (*Sida cordifolia*) found in Koide zho village, Senapati, Manipur.

Table 14: Traditional medicinal plant documentation table of Khii Tou Lou (*Sida cordifolia*).

Category	Details
1. Plant Identification	
- Local Name	Khii tou lou, Bala, flannel weed, Flannel weed, Indian country mallow
- Scientific Name	*Sida cordifolia* Family: Malvaceae
- Plant Type	Shrub
2.Traditional Uses	Traditionally used to treat fever, internal heat, stomach upset, and indigestion due

	to its antipyretic, cooling, and digestive properties.
3. Plant Part Used	
- Specific Part(s) Used	Leaves, Roots, Bark, Flowers, Seeds
- Condition of Use	Fresh
4. Collection Details	
- Locality	Koide zho village, Senapati, Manipur.
- Season/Time of Collection	13 October 2024
- Collector	Mr. Souba Thaio & Ms. H. Vaveinai
5. Preparation & Formulation	
- Other Plants or Materials Used (If any)	No
- Additives or Vehicles	Water
- Formulation Type	Decoction
6. Processing & Administration	
- Method of Processing	Boiling
- Dosage & Frequency	Twice daily
- Mode of Administration	Oral
7. Other Traditional Uses	
- Additional Ethnobotanical Uses	No
- Known Side Effects (If any)	Restlessness, insomnia, dizziness

Figure 16: Photograph of Daipah (*Rhododendron arboreum*) found in Koide zho village, Senapati, Manipur.

Table 15: Traditional medicinal plant documentation table of Daipah (*Rhododendron arboreum*).

Category	Details
1. Plant Identification	
- Local Name	Daipah, Burans, gurans
- Scientific Name	*Rhododendron arboreum* Family: *Ericaceae*
- Plant Type	Tree
2. Traditional Uses	Traditionally used to soften and facilitate the passage of bones stuck in the throat, aiding in their safe removal.
3. Plant Part Used	
- Specific Part(s) Used	Leaves, Flowers
- Condition of Use	Fresh & Dried
4. Collection Details	
- Locality	Koide Mathak Village, Senapati, Manipur.

- Season/Time of Collection	10th October, 2024
- Collector	Mr. Souba Thaio & Ms. H. Vaveinai
5. Preparation & Formulation	
- Other Plants or Materials Used (If any)	No
- Additives or Vehicles	No
- Formulation Type	
6. Processing & Administration	
- Method of Processing	Chewing
- Dosage & Frequency	Once daily
- Mode of Administration	Oral
7. Other Traditional Uses	
- Additional Ethnobotanical Uses	Timber
- Known Side Effects (If any)	Low Blood Pressure, Weakness, Nausea, Dizziness

Conclusion

The study of medicinal plants in Koide village provides profound insights into the traditional healthcare practices of the Poumai Naga tribe. The use of ethnobotanical knowledge has been an integral part of their daily lives, addressing various ailments with natural remedies passed down through generations. This documentation of 14 medicinal plant species underscores the invaluable role of indigenous knowledge in health and wellness.

The significance of traditional medicine in Koide village extends beyond its medicinal properties; it is deeply rooted in the cultural, social, and spiritual life of the Poumai Naga people. Traditional healers like Mr. Souba Thaio play a vital role in preserving and transmitting this knowledge, ensuring its continuity for future generations. However, modernization and environmental changes pose significant threats to the sustainability of such practices. Deforestation, habitat loss, and a decline in traditional knowledge transmission could lead to the gradual disappearance of these medicinal plants and their associated wisdom.

Scientific validation of these medicinal plants is necessary to integrate traditional medicine with modern healthcare systems. Ethnobotanical research can pave the way for new pharmaceutical discoveries, as many of these plants contain bioactive

compounds with significant therapeutic potential. Encouraging collaboration between traditional healers and scientific researchers can help bridge the gap between indigenous knowledge and modern medicine [5].

Furthermore, conservation efforts are crucial to safeguarding medicinal plant biodiversity. Community-based initiatives, such as the establishment of medicinal plant gardens and awareness programs, can promote sustainable harvesting practices. Government policies and local initiatives should also focus on protecting forest resources and supporting traditional healers in their efforts to preserve indigenous medicine.

This study highlights the urgent need to document and conserve traditional medicinal knowledge before it is lost. Future research should explore the pharmacological properties of these plants through biochemical analysis and clinical trials. Additionally, promoting educational programs within indigenous communities can encourage younger generations to value and continue their ancestral healing traditions.

In conclusion, the ethnobotanical knowledge of the Poumai Naga tribe in Koide village is a rich and valuable heritage that needs to be preserved and further explored. By fostering conservation efforts, promoting scientific research, and integrating traditional medicine with contemporary healthcare, we can ensure that this indigenous wisdom remains a cornerstone of sustainable healthcare practices for years to come.

Conflict of Interest: The authors have no conflict of interest. Financial or otherwise.

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Research article

STRUCTURAL AND RHEOLOGICAL PROPERTIES OF RICE STARCH FROM LOCAL VARIETIES: POTENTIAL AS NOVEL PHARMACEUTICAL EXCIPIENTS

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Abstract

Background: *Starch is a widely utilized natural excipient in pharmaceutical formulations due to its biocompatibility, biodegradability, and multifunctional roles as a binder, disintegrant, and filler.*
Objective: *This study aimed to extract and characterize starch from five local rice varieties—Joldubi, Toraboli, Huwagmoni, Mala, and Bao—cultivated in Assam, India, and evaluate their potential as pharmaceutical excipients.*
Methods: *Starch was isolated using an alkaline extraction method and subjected to comprehensive physicochemical characterization. Evaluated parameters included percentage yield, loss on drying, true and bulk density, tapped density, compressibility index, Hausner ratio, angle of repose, and particle size distribution.*
Results and Discussion: *The starches showed significant variability across rice varieties. Percentage yields ranged from 20.54% (Bao) to 24.39% (Joldubi), indicating diverse extraction efficiencies. Bao rice starch exhibited superior flow properties, with a Hausner ratio of 1.367 and an angle of repose of 41.93°, favouring direct compression suitability. Microscopy revealed particle sizes from 10.6 ± 1.71 µm (Bao) to 13.6 ± 2.64 µm (Toraboli), potentially affecting compressibility and dissolution.*
Conclusion: *Indigenous rice starches from Assam demonstrate promising excipient properties and represent sustainable, cost-effective alternatives to synthetic pharmaceutical binders. Further studies on their performance in drug-loaded tablets and comparative analysis with commercial starches are warranted.*

Keywords: Rice starch;Pharmaceutical excipients;Natural binders;Flow properties;Tablet formulation;Direct compression.

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Introduction

The pharmaceutical industry is undergoing a paradigm shift toward sustainable and biocompatible excipients, driven by increasing environmental concerns and regulatory pressures for greener pharmaceutical manufacturing processes [1]. Among natural excipients, starch has emerged as a particularly valuable material due to its abundance, biodegradability, and multifunctional properties in drug formulations[2]. As a complex carbohydrate composed of amylose and amylopectin, starch serves critical roles as a binder, disintegrant, and filler in tablet formulations[3], while also demonstrating potential in more advanced applications such as controlled drug delivery systems [4].

While conventional starch sources like maize, potato, and tapioca have been extensively characterized for pharmaceutical use[5], indigenous rice varieties from specific geographical regions remain largely unexplored despite their potential to offer unique functional properties and economic advantages [6]. This study focuses on five traditional rice varieties-Joldubi, Toraboli, Huwagmoni, Mala, and Bao-cultivated in the Assam region of India, an area renowned for its rich biodiversity of rice cultivars [7]. These varieties were selected based on their historical use in local communities, distinctive grain characteristics[8], and preliminary evidence suggesting superior starch content compared to commercial varieties.

The investigation is grounded in the hypothesis that these indigenous rice starches possess physicochemical properties that may equal or surpass those of currently used pharmaceutical starches[9], particularly in terms of binding capacity, compressibility, and flow characteristics[10]. The alkaline extraction method was employed for starch isolation, chosen for its effectiveness in protein removal and starch purity while maintaining the structural integrity of starch granules [11].

The significance of this research extends beyond mere material characterization. First, it addresses the growing need for sustainable excipients in pharmaceutical manufacturing by evaluating locally available, renewable resources [12]. Second, it contributes to the valorisation of underutilized agricultural products [13], potentially creating new economic opportunities for regional farmers. Third, it provides crucial data that could help reduce reliance on imported excipients in developing countries [14]. The study comprehensively evaluates key parameters including extraction yield, moisture content, density profiles, powder flow properties, and particle size distribution-all critical factors in determining pharmaceutical applicability [15].

Furthermore, this work aligns with several United Nations Sustainable Development Goals, particularly those related to responsible consumption and

production (SDG 12) and industry innovation (SDG 9) [16]. The findings may have broader implications for pharmaceutical formulation science, potentially leading to the development of novel excipient systems or co-processed excipients based on these rice starches [17]. Future research directions could explore their behavior in direct compression formulations, compatibility with various APIs, or potential modifications to enhance specific functional properties [18]. By bridging traditional agricultural knowledge with modern pharmaceutical science, this study opens new possibilities for the development of culturally relevant and environmentally friendly pharmaceutical products [19].

Materials and Methods

1. Sample Collection and Preparation

The study investigated five indigenous rice varieties (*Oryza sativa* L.) - Joldubi, Toraboli, Huwagmoni, Mala, and Bao - collected from farmers in Dhemaji District, Assam, India (27°05'27"N to 27°57'16"N latitude; 94°12'18"E to 95°41'32"E longitude) during October 2023. Following collection, botanical authentication was performed by Dr. N. Odyuo at the Botanical Survey of India, Shillong, with herbarium voucher specimens deposited (Accession Numbers: DU/PSc/PR/01/2024 to DU/PSc/PR/05/2024).

For sample preparation, harvested grains underwent a rigorous cleaning process using a vibratory sieve shaker with sequential 4mm and 2mm mesh screens to remove field debris and impurities. The cleaned grains were triple-rinsed with deionized water at 25±2°C to eliminate surface contaminants. Subsequent sun-drying was conducted on stainless steel trays (2cm bed depth) for 7 days under ambient conditions (32±5°C, 65±10% RH), with periodic manual turning to ensure uniform drying. Processed samples were stored in multilayer barrier bags (PET/Al/PE) with oxygen absorbers at 4°C until extraction to preserve quality.

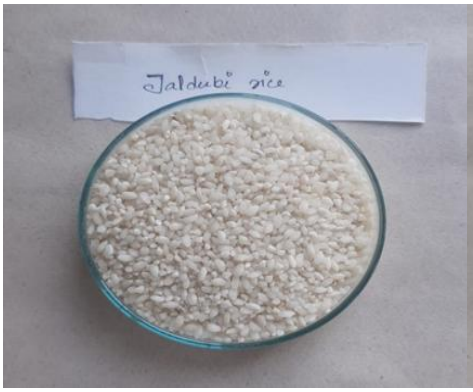

Figure 1: Joldubi rice.

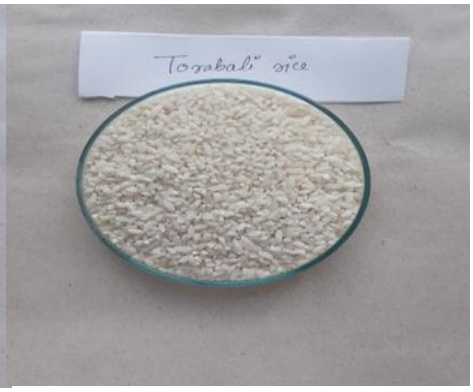

Figure 2: Toraboli rice.

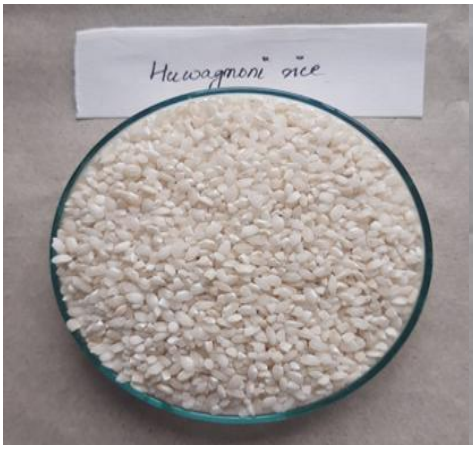

Figure 3: Huwagmoni rice.

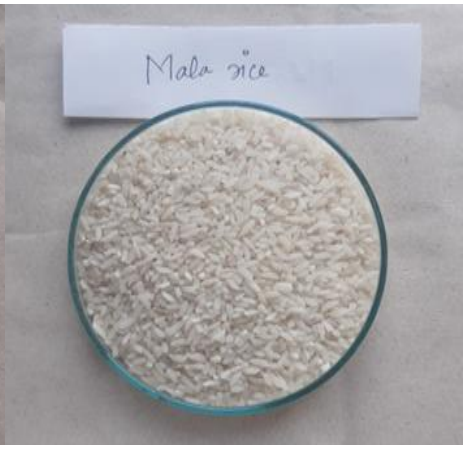

Figure 4:Mala rice.

Figure 5: Bao rice.

2. Starch Extraction Protocol

The alkaline extraction method was optimized based on established protocols with modifications [3] for local rice varieties. The extraction process commenced with alkaline steeping, where 800g aliquots of each rice variety were immersed in 1600mL of 0.4% (w/v) NaOH solution containing 0.01% sodium metabisulfite as an antioxidant. This mixture was maintained at 50±1°C in a thermostatically controlled water bath for 24 hours, with continuous pH monitoring and adjustment to maintain optimal extraction conditions at pH 10.5±0.2. The steeping solution was replaced every 8 hours to prevent microbial proliferation and maintain extraction efficiency.

Following steeping, the softened grains underwent wet milling operated at 3000 rpm for 5 minutes to facilitate starch release. The resultant slurry was subjected to sequential vacuum filtration (Buchner funnel) through a graded series of stainless steel sieves (500µm → 250µm → 125µm) using Whatman #4 filter paper. The filtrate was then centrifuged at 4°C for 4 hours to achieve complete starch

sedimentation. The starch pellet underwent a comprehensive purification process involving three washing cycles with 0.1M NaOH (3× volumes), followed by rinsing with deionized water until neutral pH was achieved, and final dehydration with absolute ethanol. The purified starch was dried in a forced-air oven at 55±2°C for 24 hours, with the final product sieved through a 125μm mesh to ensure particle size uniformity.

3. Identification of Starch

The presence of starch in all samples was confirmed using an iodine test, where a blue-black color indicated starch [22].

4. Physicochemical Characterization

4.1 Percentage Yield:

$$Percentage\ \text{yield} = \frac{\text{Mass of extracted starch}}{\text{Mass of initial rice}} \times 100$$

4.2 Loss on Drying (LOD): Determined by drying 1–2 g of starch at 105°C for 4 hours [23].

$$\%\ \text{of Loss on drying} = \frac{\text{Weight loss}}{\text{Weight of sample}} \times 100$$

4.3 True Density: Measured using a glass pycnometer with benzene as the displacement liquid [24].

$$\text{True density} = \frac{W2 - W1}{W4 - W2}$$

Where, W1 = pycnometer weight,
W2 =pycnometer + sample,
W4 =pycnometer + sample + solvent.

4.4 Bulk and Tapped Density: Evaluated using a 50 mL graduated cylinder [25].

$$\text{Bulk density} = \frac{\text{Weight of powder (g)}}{\text{Bulk volume (mL)}}$$

Tapped density was measured after 500 taps using a densitometer.

$$\text{Tapped Density} = \frac{\text{Weight of powder}}{\text{Tapped volume}}$$

4.5 Compressibility Index and Hausner Ratio:

$$\text{Compressibility Index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}}$$

$$\text{Hausner Ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Table 1: The generally accepted scale of flowability for the compressibility index and the Hausner ratio

Carr's index	Flowability	Hausner ratio
≤10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
≥38	Very Very poor	>1.60

4.6 Angle of Repose: Determined by the fixed funnel method [20].

$$\tan\theta = \frac{h}{r}$$

where, h = pile height,
r = radius.

Table 2:The generally accepted scale of flowability for angle of repose

Flow properties	Angle of repose
Excellent	25 -30
Good	31 -35
Fair	36 -40
Passable	41 – 45

Poor	46-55
Very poor	56- 65
Poorest	More than 66

4.7 Particle Size: Analyzed microscopically (Olympus, Japan) by measuring 600 particles per sample [26].

5. Statistical Analysis

All experiments were performed in triplicate, and data are presented as mean ± standard deviation (SD).

Results and Discussion

1. Percentage Yield of Starch Extraction

The percentage yield of starch extracted from the five rice varieties varied significantly (Table 3).

Table 3: Percentage yield of rice starch(Mean±SD of n=3)

Rice starch	Percentage yield(w/w)
Joldubi rice	24.39±0.39
Toraboli rice	22.13±0.29
Huwagmoni rice	22.84±0.45
Mala rice	22.43±0.31
Bao rice	20.54±0.22

Joldubi rice exhibited the highest yield (24.39 ± 0.39%), while Bao rice showed the lowest (20.54 ± 0.22%). These differences can be attributed to variations in starch content among the rice varieties, influenced by genetic factors and cultivation conditions. The alkaline extraction method employed in this study was effective in isolating starch, with yields comparable to those reported in previous studies for other rice varieties [3] [6].

2. Loss on Drying (LOD)

The LOD values indicated the moisture content of the extracted starches (Table 4).

Table 4: Values of the LOD (Mean±SD of n=3).

Rice starch	Loss on drying(g)
Joldubi rice	10.77 ± 0.42

Toraboli rice	12.23 ± 0.27
Huwagmoni rice	6.24 ± 0.18
Mala rice	7.13 ± 0.26
Bao rice	8.2 ± 0.11

Joldubi rice starch had the highest LOD (10.77 ± 0.42%), suggesting a higher residual moisture content, which may affect its stability during storage. In contrast, Huwagmoni rice starch showed the lowest LOD (6.24 ± 0.18%), indicating better shelf stability. These results align with findings by Khalid et al. (2017), who noted that moisture content is critical for starch stability and functionality in pharmaceutical applications.

3. True Density and Bulk Density

True density and bulk density measurements are presented in Tables 5.

Table 5: Values of the True density and Bulk density (Mean±SD of n=3).

Rice starch	True density(g/ml)	Bulk density(g/ml)
Joldubi rice	0.0721±0.003	0.3021±0.016
Toraboli rice	0.0523±0.002	0.2834±0.002
Huwagmoni rice	0.0532±0.004	0.3151±0.013
Mala rice	0.0731±0.003	0.2923±0.011
Bao rice	0.0621±0.012	0.4011±0.020

Joldubi and Mala rice starches had the highest true density values (0.0721 ± 0.003 g/ml and 0.0731 ± 0.003 g/ml, respectively), indicating a compact particle structure. Bao rice starch exhibited the lowest true density (0.0621 ± 0.012 g/ml), suggesting a more porous structure. Bulk density followed a similar trend, with Bao rice starch showing the highest bulk density (0.4011 ± 0.020 g/ml), likely due to its larger particle size and lower cohesiveness [27].

4. Tapped Density and Flow Properties

Tapped density, Compressibility Index and Hausner ratio results are shown in Table 6.

Table 6: Values of the Tapped density, Compressibility index and Hausner ratio (Mean±SD of n=3).

Rice starch	Tapped density(g/ml)	Compressibility Index	Hausner Ratio
Joldubi rice	0.5311±0.040	40.447±0.723	1.847±0.045
Toraboli rice	0.5330±0.003	31.363±0.790	1.763±0.121

Huwagmoni rice	0.5171±0.012	41.257±0.555	1.677±0.025
Mala rice	0.5092±0.009	41.943±1.306	1.517±0.252
Bao rice	0.5351±0.026	26.777±1.017	1.367±0.076

Tapped density was highest for Bao rice starch (0.5351 ± 0.026 g/ml), reflecting its better compaction properties. The compressibility index and Hausner ratio were used to evaluate flowability. Joldubi and Huwagmoni rice starches exhibited poor flowability (compressibility index > 40%, Hausner ratio > 1.6), while Bao rice starch showed the best flow properties (compressibility index: 26.777 ± 1.017%, Hausner ratio: 1.367 ± 0.076). These findings are consistent with the classification scale for powder flowability [28].

5. Angle of Repose

The angle of repose results are presented in Table 7.

Table 7: Values of the Angle of repose (Mean±SD of n=3).

Rice starch	Angle of Repose
Joldubi rice	42.840±0.617
Toraboli rice	46.133±0.236
Huwagmoni rice	41.283±0.631
Mala rice	42.067±0.284
Bao rice	41.933±0.525

The angle of repose ranged from 41.283 ± 0.631° (Huwagmoni rice) to 46.133 ± 0.236° (Toraboli rice), indicating fair to poor flowability. These results suggest that additional excipients or processing aids may be required to improve flow during tablet manufacturing [20].

6. Particle Size Analysis

Particle size distribution results are shown in Table 8.

Table 8: Values of the Particle-Size (Mean±SD of n=3).

Rice starch	Particle-Size (μm)
Joldubi rice	11±1.51
Toraboli rice	13.6±2.64
Huwagmoni rice	12.7±2.04
Mala rice	12.2±1.29
Bao rice	10.6±1.71

Particle size analysis showed that Toraboli rice starch had the largest particles (13.6 ± 2.64 µm), while Bao rice starch had the smallest (10.6 ± 1.71 µm). Smaller particle sizes are generally associated with better compressibility and binding properties, as noted by Pitt et al. (2013).

The physicochemical properties of the starches extracted from the five rice varieties demonstrated significant variability, which can be leveraged for specific pharmaceutical applications. For instance, Bao rice starch, with its favorable flow and compaction properties, is suitable for direct compression tablet formulations. In contrast, Joldubi and Huwagmoni rice starches, despite their poor flowability, may serve as effective binders due to their higher cohesiveness.
The alkaline extraction method proved efficient for starch isolation, yielding products with properties comparable to commercially available starches. However, the high moisture content in some starches (e.g., Joldubi rice) necessitates careful drying and storage to prevent degradation. The structural diversity observed in the starches, such as variations in particle size and density, underscores the importance of selecting the appropriate starch type based on the desired excipient functionality.
These findings contribute to the growing body of research on natural excipients, highlighting the potential of locally sourced rice starches as sustainable alternatives to synthetic binders in pharmaceutical formulations [2] [21].

Conclusion

The present study successfully characterized starch extracted from five local rice varieties—Joldubi, Toraboli, Huwagmoni, Mala, and Bao—for potential use as pharmaceutical excipients. The alkaline extraction method proved effective in isolating starch with yields ranging from 20.54% to 24.39%, demonstrating the feasibility of utilizing these indigenous rice varieties as sustainable sources of starch.

Key physicochemical properties, including moisture content (LOD: 6.24–12.23%), true density (0.0523–0.0731 g/ml), bulk density (0.2834–0.4011 g/ml), and flow characteristics (compressibility index: 26.78–41.94%; Hausner ratio: 1.37–1.85), revealed significant variations among the starches. Bao rice starch exhibited the most favorable flow and compaction properties, making it a promising candidate for direct compression tableting. In contrast, Joldubi and Huwagmoni starches, despite their poor flowability, displayed strong binding potential due to their cohesive nature.

Particle size analysis (10.6–13.6 µm) and angle of repose (41.28°–46.13°) further supported the functional diversity of these starches, highlighting their suitability for different pharmaceutical applications. The findings align with previous studies emphasizing the role of starch structure in drug formulation performance [2] [21].

This study underscores the potential of locally sourced rice starches as cost-effective, biodegradable alternatives to synthetic excipients. Future research should explore modifications (e.g., pregelatinization, co-processing) to enhance functionality and evaluate their performance in specific dosage forms.

Conflict of Interest

The authors have no conflict of interest to declare.

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Review article

VIROSOMES AS A NOVEL NANOCARRIER FOR TARGETED DRUG DELIVERY

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Abstract

Background: *Targeted drug delivery systems incorporating nanotechnology have been the key focus of modern medicine as they aim to improve therapeutic efficacy along with minimizing possible side effects. Among the various nanocarriers used, virosomes have emerged as a promising candidate due to their ability to mimic viruses for implementation in targeted drug delivery without causing infections. Due to their biocompatibility and versatility, they can efficiently enter specific cells making them highly suitable for site-specific drug and vaccine delivery.*

Objective: *The objective of this review is to explore the potential of virosomes as a nanocarrier while discussing their structural characteristics, functional advantages and recent advancements in virosome-based drug delivery.*

Methods: *An extensive literature survey was carried out through various databases like Google Scholar, Pubmed, Sciencedirect, etc. to support this review. The primary focus was on virosome formulation, mechanisms of drug delivery, and therapeutic applications, particularly in areas like cancer and gene therapy.*

Discussions: *From the survey that was carried out, it was found that virosomes offer several advantages over traditional drug delivery systems. Their biocompatibility, ability to cross biological barriers and evade immune detection makes them superior to conventional nanocarriers.*

Conclusion: *Virosomes hold great promise as a novel and versatile nanocarriers system for targeted drug delivery. However, challenges including large-scale production, stability, and immune response modulation require further modifications and optimization. Future research should focus on overcoming the*

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mentioned challenges so that virosomes could become a prime technology in targeted drug delivery, offering safer and more effective treatment options for various diseases.

Keywords: Virosomes, Gene therapy, Targeted drug delivery, Cancer therapy, Nanocarriers

Introduction

The continuous advancement of nanotechnology has revolutionized the field of drug delivery, enabling precise and efficient therapeutic interventions while minimizing systemic toxicity. Among the various nanocarrier systems developed, virosomes have emerged as a promising platform for targeted drug delivery due to their unique structural and functional properties [1]. Virosomes are artificially engineered virus-like lipid vesicles that incorporate viral envelope proteins into a phospholipid bilayer while being devoid of viral genetic material. This ensures that they retain the ability of viruses to efficiently fuse with host cell membranes, facilitating intracellular drug delivery without the risks associated with live viral vectors [2].

One of the most significant advantages of virosomes is their biocompatibility and versatility in drug delivery applications. Unlike conventional liposomes, virosomes mimic viral entry mechanisms, enabling efficient cellular uptake while reducing immune recognition[3]. Their structural adaptability allows for surface modifications with targeting ligands, antibodies, or peptides, facilitating site-specific drug delivery to diseased tissues, including cancerous tumors and infected cells[4]. These properties make virosomes particularly attractive in various biomedical fields, including oncology, vaccine development, gene therapy, and infectious disease treatment[5].

Virosomes have demonstrated remarkable potential in vaccine development, where they act as immune adjuvants, enhancing both humoral and cellular immune responses[1]. The success of virosome-based vaccines, such as those developed for influenza and hepatitis A, highlights their safety and efficacy in human applications [6]. Moreover, their potential in RNA and gene therapy has garnered increasing attention, particularly for mRNA-based therapeutics and siRNA delivery, which require efficient cellular entry and cytoplasmic release [7].

Despite these advantages, virosome-based drug delivery still faces challenges, including stability concerns, large-scale production complexities, and potential immunogenicity in certain applications[5]. However, ongoing research in bioengineering and nanomedicine is actively addressing these limitations,

improving virosomal formulations for enhanced therapeutic efficacy [8]. Given their biophysical advantages, targetability, and safety, virosomes represent a cutting-edge nanocarrier system with immense potential for next-generation precision medicine.

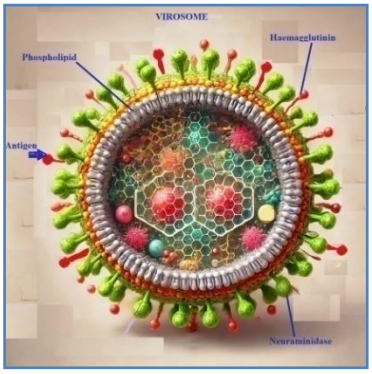

Figure 1: Components of virosome

Type of virosomes

Influenza virus reconstituted Virosome

Influenza virus reconstituted virosomes (IRVs) are lipid-based vesicles that are created by embedding the viral envelope proteins, such as hemagglutinin (HA) and neuraminidase (NA), into a phospholipid bilayer. This reconstitution process enables the virosomes to mimic the properties of the influenza virus while removing the viral genetic material, making them safe for use in drug delivery and vaccine applications.

The reconstituted influenza virus components on the surface of the virosome facilitate interactions with host cell membranes, enabling fusion and the delivery of encapsulated bioactive agents, such as nucleic acids, proteins, and small molecules, directly to target cells. The hemagglutinin protein on the virosome surface binds to sialic acid receptors on the host cell surface, promoting the fusion of the virosome with the cell membrane. This mechanism allows for efficient cellular uptake and delivery of the virosome's contents.

Due to their ability to enhance the targeted delivery of therapeutic agents and their strong immunogenic potential, IRVs are explored for use in gene therapy, vaccine

development, and drug delivery systems [14]. Their safety, stemming from the absence of viral genetic material, makes them a promising alternative to traditional viral vectors in clinical applications.

Hemagglutinating Virus reconstituted Virosome

Hemagglutinating Virus Reconstituted Virosomes (HV-RVs) are lipid-based vesicles that incorporate viral envelope proteins, such as hemagglutinin (HA) and neuraminidase (NA), into a phospholipid bilayer. This reconstitution process allows the virosomes to mimic the properties of the original virus, enabling them to interact with host cell membranes through the viral glycoproteins. The viral components on the surface of the virosome allow for the fusion with target cells, facilitating the delivery of bioactive agents, such as proteins, nucleic acids, or small molecules, into cells. The hemagglutinin protein binds to sialic acid receptors on the host cell surface, promoting cellular uptake of the virosome.

HV-RVs are used as drug delivery systems and in vaccine development due to their ability to safely deliver therapeutic agents without the presence of viral genetic material, thus eliminating the risk of viral replication. The viral proteins embedded in the lipid membrane ensure the stability of the virosomes and allow for controlled release and targeted delivery of therapeutic molecules.

Preparation of virosomes

General method to formulate Virosome

The formulation of virosomes involves the incorporation of viral envelope proteins into liposomal structures, which allows for the targeted delivery of bioactive agents. The general method includes the following steps:

i) *Preparation of Liposomes:*Liposomes are typically created by dissolving phospholipids, such as phosphatidylcholine and cholesterol, in an organic solvent (e.g., chloroform or methanol) and then evaporating the solvent to form a thin lipid film. This film is subsequently hydrated with an aqueous buffer to produce multilamellar vesicles (MLVs). These MLVs are then processed through techniques like sonication or extrusion to form unilamellar vesicles (ULVs), which are more suitable for drug delivery [9].

ii) *Reconstitution of Viral Glycoproteins*: The viral glycoproteins (such as hemagglutinin and neuraminidase) are purified from the virus, and then incorporated into the liposomal membrane. This reconstitution occurs

through the incubation of the liposomes with the viral proteins under specific conditions that promote fusion of the viral glycoproteins with the lipid bilayer [10]. Detergents or other solubilizing agents may be employed to assist in protein insertion [11].

iii) *Removal of Detergent (if used)*: If detergents were used during the reconstitution step, they must be removed to ensure the structural integrity of the virosomes. This is typically achieved through dialysis or by adsorption onto a resin, which facilitates the detachment of the detergent while ensuring the successful incorporation of the viral glycoproteins into the liposomes [11].

iv) *Size Reduction and Purification*: After the reconstitution, the virosomes are often purified to eliminate excess viral proteins and other unincorporated components. Techniques like density gradient centrifugation or gel filtration chromatography are used to isolate pure virosomes. The size of the virosomes is typically controlled by extrusion, which results in vesicles with a consistent size range, typically between 50–200 nm in diameter [9].

v) *Encapsulation of Therapeutic Agents*: Bioactive agents such as nucleic acids, proteins, or small molecules can be encapsulated within the virosomes. This can be done either during the liposome formation process or through post-insertion methods, which ensures that the therapeutic cargo is protected and can be delivered efficiently to target cells [12].

vi) *Characterization*: The virosome formulations are then characterized to assess size, charge, encapsulation efficiency, and stability. Standard techniques include dynamic light scattering (DLS) for particle size analysis, zeta potential measurement for charge determination, and electron microscopy for structural analysis [11].

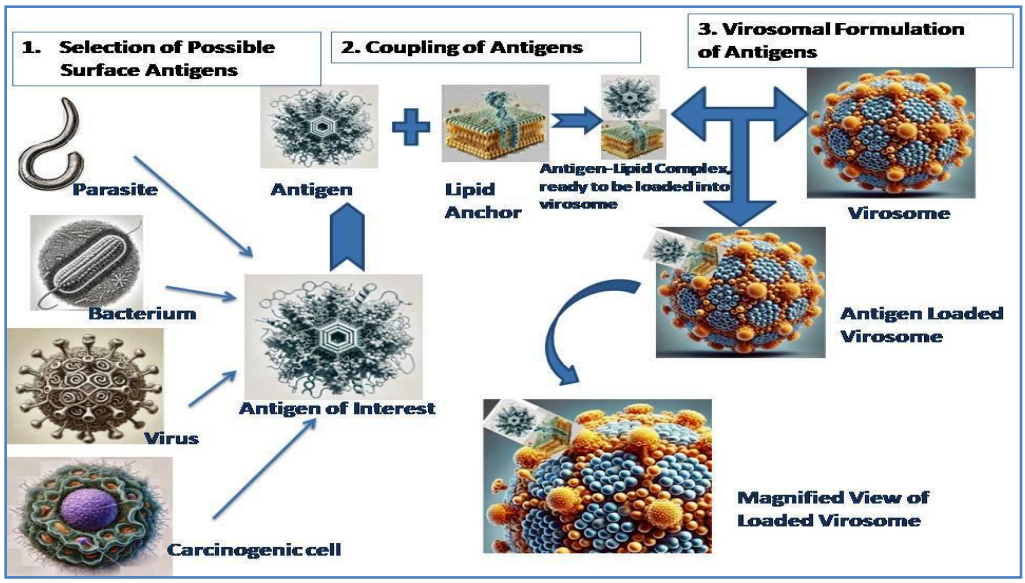

Figure 2: General method for preparation of virosomes

Optimization of Virosomes

The optimization of virosomes involves fine-tuning several key parameters to enhance their efficiency and stability for drug and gene delivery applications. These parameters include the composition of liposomes, the reconstitution of viral glycoproteins, encapsulation efficiency, and size control. Several strategies have been developed to optimize these factors.

Lipid Composition

The lipid composition of the liposomes is a critical factor in the formulation of virosomes. The balance between different lipids, such as phosphatidylcholine, cholesterol, and sphingolipids, influences the fluidity, stability, and fusion ability of the virosomes. The incorporation of cholesterol into the liposomal membrane, for instance, enhances membrane stability and helps maintain the virosome structure during storage and upon fusion with the target cell membrane [11]. Additionally, incorporating lipids with specific properties, such as fusogenic lipids, can improve the ability of virosomes to merge with cellular membranes [9].

Reconstitution of Viral Glycoproteins

The efficiency of viral glycoprotein incorporation into the lipid membrane is a key factor in virosome optimization. The optimal protein-to-lipid ratio and conditions

for protein insertion, including temperature, pH, and ionic strength, must be carefully controlled. It has been shown that the incorporation of hemagglutinin (HA) into the lipid bilayer should be optimized to ensure high levels of protein fusion activity while maintaining membrane integrity [11]. Additionally, the use of detergents during the reconstitution step must be optimized to ensure efficient protein incorporation without compromising the virosome structure [11].

Encapsulation Efficiency

To achieve optimal drug delivery, the encapsulation efficiency of bioactive agents within virosomes needs to be maximized. This is often achieved by adjusting the liposome formation conditions, such as lipid concentration and hydration conditions, as well as by using techniques like reverse-phase evaporation or extrusion. Optimization of these parameters ensures that a high proportion of the active agent is successfully encapsulated within the virosomes, increasing their therapeutic potential [12].

Size and Surface Charge Optimization

The size and surface charge of virosomes significantly affect their cellular uptake, stability, and biodistribution. Virosomes with an optimal size range (typically between 50–200 nm) are more likely to be internalized efficiently by cells via endocytosis. The surface charge of the virosomes also plays a role in determining their interaction with the negatively charged cell membranes. A neutral or slightly anionic surface charge is often preferred to avoid non-specific interactions and enhance target specificity [9]. Size reduction is typically achieved through extrusion or sonication, and surface charge can be modified by incorporating charged lipids or using surface coatings [11].

Stability and Storage Conditions

Virosomes must be stable during storage and transportation to ensure their effectiveness upon use. The addition of stabilizing agents, such as sucrose or trehalose, can help protect the virosomes from degradation during freeze-drying or long-term storage. Stability can also be enhanced by optimizing the lipid composition and minimizing the presence of free detergents or unincorporated viral proteins [12].

Comparison between virosome and liposomes

Virosomes and liposomes are both lipid-based vesicles used in drug delivery, but they have distinct characteristics and applications due to their structural differences. Below is a detailed comparison between virosomes and liposomes:

- ***Structure***

Virosomes: Virosomes are liposome-like vesicles that incorporate viral envelope proteins, such as hemagglutinin (HA) and neuraminidase (NA), into their lipid bilayer. These proteins enable virosomes to mimic the properties of the virus, allowing them to interact with host cell membranes through specific receptor recognition, facilitating fusion and efficient delivery of their cargo. Importantly, virosomes lack the viral genetic material, which makes them non-replicative and safe for therapeutic use [11].

Liposomes: Liposomes are lipid vesicles composed solely of phospholipids and cholesterol that self-assemble into bilayer structures when hydrated. Liposomes do not contain any viral proteins and are mainly used as non-viral drug carriers. The lipid composition of liposomes can be customized to enhance the stability, size, and charge, but they lack the inherent fusogenic properties that virosomes possess [9].

- ***Mechanism of Cellular Uptake***

Virosomes: Virosomes utilize viral glycoproteins (e.g., hemagglutinin) on their surface to bind specifically to host cell receptors, such as sialic acid on the cell membrane. This binding facilitates fusion between the virosome and the host cell, allowing for the direct delivery of encapsulated bioactive agents [13]. The viral proteins mimic a viral infection process, enhancing targeted cellular uptake.

Liposomes: Liposomes rely on non-specific mechanisms such as endocytosis for cellular uptake. The process of internalization typically occurs through receptor-mediated endocytosis or phagocytosis, depending on the type of liposome and its surface characteristics [12]. However, liposomes do not inherently have the fusogenic properties that virosomes do, meaning that additional modifications are required to enhance their cellular uptake.

- ***Drug Delivery Efficiency***

Virosomes: Virosomes are highly efficient in delivering bioactive agents to targeted cells due to their ability to fuse with the target cell membrane. The viral proteins on their surface ensure that the virosomes can specifically target certain cells, which makes them highly effective for gene therapy, vaccine delivery, and targeted drug delivery [11]. Their fusogenic properties provide a more efficient means of internalizing cargo into the cell.

Liposomes: Liposomes are effective carriers for a variety of drug formulations but are generally less efficient in drug delivery compared to virosomes, especially when it comes to targeted delivery. While liposomes can encapsulate a broad range of molecules, they often require surface modifications (e.g., coating with antibodies or targeting ligands) to enhance specificity for particular cell types [9].

- ***Safety Profile***

Virosomes: Since virosomes do not contain viral genetic material, they do not replicate and therefore have a reduced risk of causing viral infections. They are generally considered safe for use in therapeutic applications, such as vaccines, gene therapy, and drug delivery, because the viral components are incorporated in a way that does not pose a risk of inducing viral replication or genetic modification [11].

Liposomes: Liposomes are considered to have a favorable safety profile as they do not contain any viral components. The risk of immunogenicity is relatively low, and liposomes have been extensively studied for a variety of clinical applications. However, liposome formulations can sometimes elicit immune responses, depending on the lipid composition, surface charge, and other factors [12].

- ***Applications***

Virosomes: Virosomes are primarily used in the delivery of vaccines, gene therapy, and other therapeutic applications requiring targeted drug delivery. They are also explored as adjuvants for immune responses due to their ability to mimic viral infection processes [11]. The presence of viral proteins on their surface enhances their immunogenic potential, making them effective for vaccine formulations.

Liposomes: Liposomes are widely used for drug delivery, including the delivery of anticancer drugs, antibiotics, and gene therapies. They are also utilized in cosmetics

and other industries. Liposomes can deliver a variety of payloads, including hydrophobic and hydrophilic compounds, but they do not have the same targeted delivery capabilities as virosomes without further modification [9].

- ***Stability***

Virosomes: Virosomes are generally stable but can be sensitive to environmental conditions, such as temperature and pH. Their stability can be enhanced through lyophilization (freeze-drying) or by adding stabilizing agents like sucrose [12].

Liposomes: Liposomes, depending on their composition, can be less stable than virosomes, particularly when exposed to extremes in pH, temperature, or ionic strength. However, they are stable under many conditions and can be freeze-dried for long-term storage. Liposome formulations also benefit from stabilization techniques, including the use of cryoprotectants and surface coatings [9].

- ***Cost of Production***

Virosomes: The production of virosomes is typically more complex and expensive than liposomes due to the additional step of incorporating viral proteins into the liposome. The need for virus purification, protein extraction, and reconstitution adds to the cost [11].

Liposomes: Liposome production is relatively straightforward and less expensive than virosome production, as it does not require viral protein extraction or complex reconstitution steps. Liposomes can be easily produced in large quantities, making them more cost-effective for many applications [9].

Table 1: Comparison of virosomes and liposomes

Feature	**Virosomes**	**Liposomes**
Structure	Lipid vesicles with viral proteins	Lipid vesicles without viral proteins
Mechanism of Uptake	Receptor-mediated fusion with cells	Endocytosis or phagocytosis
Drug Delivery Efficiency	High, due to fusogenic properties	Moderate, unless modified for targeting

Safety Profile	Safe, non-replicative	Safe, but can trigger immune responses
Applications	Vaccines, gene therapy, targeted drug delivery	General drug delivery, gene therapy, cosmetics
Stability	Sensitive to conditions but stabilizable	Generally stable, can be stabilized further
Cost of Production	Higher, due to viral protein incorporation	Lower, simpler production process

Characteristics of virosomes

Virosomes are lipid-based vesicles that incorporate viral glycoproteins into their structure, allowing them to mimic viral infection processes while delivering bioactive agents. These characteristics make virosomes particularly effective for targeted drug delivery, gene therapy, and vaccine applications. Below are the key characteristics of virosomes:

i) *Lipid Bilayer Structure:* Virosomes consist of a lipid bilayer, similar to liposomes, which is composed of phospholipids, cholesterol, and sometimes other lipids. The bilayer encapsulates the virosome's bioactive cargo (such as proteins, peptides, or nucleic acids). The lipid composition of the bilayer influences the stability, fluidity, and fusion ability of virosomes [9].

ii) *Incorporation of Viral Glycoproteins:* A hallmark feature of virosomes is the incorporation of viral envelope glycoproteins, such as hemagglutinin (HA) and neuraminidase (NA), into the lipid bilayer. These glycoproteins enable virosomes to mimic the behavior of viruses by recognizing and binding to specific cell surface receptors, facilitating membrane fusion with target cells [11]. This feature allows for highly efficient and specific drug and gene delivery.

iii) *Fusogenic Properties:*The viral glycoproteins incorporated into virosomes, particularly the fusion protein (like HA), impart fusogenic properties to the vesicles. This allows virosomes to merge with the host cell membrane, facilitating the direct release of their payload into the cell cytoplasm, which is crucial for efficient drug delivery or gene transfer [11].

iv) *Targeted Delivery:* Virosomes can be engineered to target specific cell types. The viral glycoproteins on the surface of the virosomes allow for receptor-mediated targeting, ensuring that the virosomes preferentially bind

to and fuse with cells that express the appropriate receptors [9]. This makes virosomes ideal for applications such as targeted vaccine delivery, gene therapy, and cancer treatment.

v) *No Replicative Potential:* Although virosomes incorporate viral glycoproteins, they do not contain the viral genome and therefore lack replicative potential. This eliminates the risk of generating infectious viruses. As a result, virosomes are considered safe for therapeutic use and are often employed in vaccine formulations and other drug delivery systems [11].

vi) *Encapsulation Capacity:* Virosomes are capable of encapsulating a wide range of bioactive agents, including nucleic acids (e.g., DNA, RNA), proteins, peptides, and small molecules. This versatile encapsulation ability makes them suitable for diverse therapeutic applications, including gene therapy, protein delivery, and targeted chemotherapy [9].

vii) *Immunogenicity:* The viral glycoproteins present on virosomes are known to induce immune responses similar to those seen in natural viral infections. This property is especially beneficial in vaccine development, as virosomes can act as adjuvants, enhancing immune system activation without the need for additional immune-stimulating agents [11]. The immunogenicity of virosomes can be modulated based on the type of viral proteins used and the formulation of the vesicle.

viii) *Biodegradability:* Virosomes, like liposomes, are biodegradable, meaning they are broken down by natural cellular processes after fulfilling their therapeutic function. This biodegradability ensures minimal toxicity and reduces the long-term accumulation of the carrier in the body [9].

ix) *Stability:* Virosomes are generally stable under appropriate storage conditions, but like all liposomal formulations, their stability can be influenced by factors such as temperature, pH, and the presence of stabilizing agents. Techniques like lyophilization (freeze-drying) can be employed to enhance the long-term stability of virosomes, making them suitable for clinical and commercial applications [12].

x) *Non-viral Alternative for Gene and Drug Delivery:* Virosomes offer a safer alternative to viral vectors for gene and drug delivery. Unlike viral vectors, which may pose risks related to immunogenicity, insertional mutagenesis, or uncontrollable replication, virosomes are non-replicative and can be engineered to be less immunogenic, making them a promising option for gene therapy and other therapeutic applications [9].

xi) *Versatility in Application:* Virosomes can be used in a wide variety of applications, including:

- Vaccine delivery: As a carrier for viral antigens, virosomes are used to create vaccines that mimic natural viral infection, stimulating strong immune responses.
- Gene therapy: Virosomes can deliver nucleic acids, such as plasmid DNA or RNA, into target cells for gene therapy applications.
- Targeted drug delivery: Virosomes can encapsulate and deliver therapeutic drugs directly to specific tissues or cells, especially in cancer treatment or targeted therapies [11].

xii) *Production Methods:* Virosomes are produced by reconstituting viral envelope proteins into liposomes. This process involves the use of detergents to extract and incorporate viral glycoproteins into the liposomal bilayer. Once the viral proteins are incorporated, detergents are removed, and the virosomes are purified and characterized for their size, encapsulation efficiency, and stability [9].

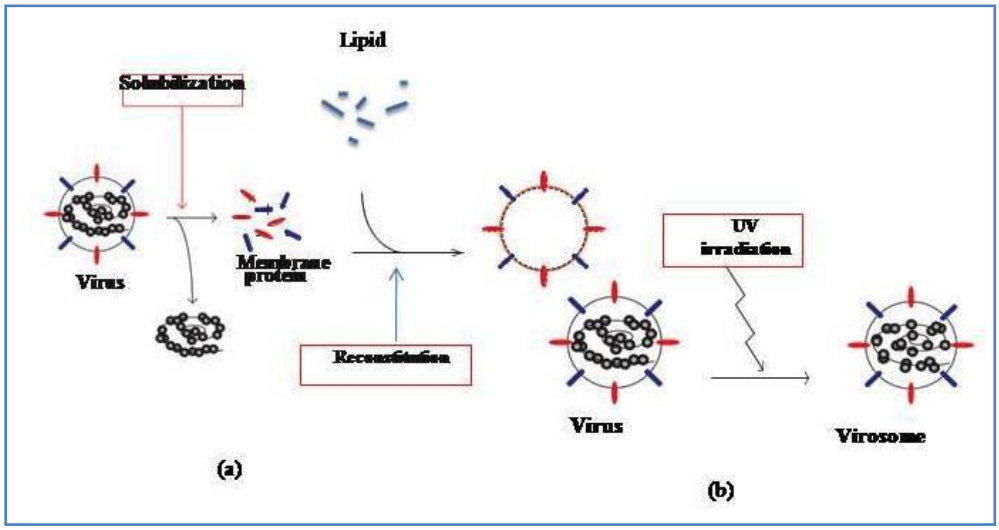

Figure 3: Formation of virosomes

(a) Reconstituted envelope containing viral envelope proteins. The solubilization of viral membrane from modified viral envelope and reconstituted with viral protein and exogenous lipids. (b) Viral envelope particles. Virus is inactivated with UV irradiation leading the fragmentation of viral genome.

Fusion Characteristics of Virosomes

The fusion characteristics of virosomes are key to their function as efficient drug delivery systems, as they facilitate the targeted delivery of bioactive agents to the cytoplasm of the host cell. These fusion properties are primarily mediated by viral

glycoproteins incorporated into the virosome structure. Below are the key aspects of the fusion characteristics of virosomes:

Fusion Mechanism

i) Receptor-Mediated Fusion: Virosomes mimic the natural infection process of viruses, where the viral envelope glycoproteins interact with specific receptors on the host cell surface. The fusion of virosomes with the cell membrane is a receptor-mediated event driven by the interaction between the viral glycoproteins (such as hemagglutinin) and cell surface receptors (such as sialic acid or other glycoproteins) [11]. This interaction triggers the conformational change of the viral glycoprotein, enabling fusion with the host cell membrane.

ii) Fusogenic Proteins: The key glycoprotein responsible for fusion in virosomes is usually **hemagglutinin (HA)**, a protein found in many viruses, such as influenza. HA mediates the fusion of the virosome membrane with the host cell membrane. Upon binding to specific cell surface receptors, HA undergoes a conformational change that facilitates membrane fusion. This process results in the virosome's cargo being delivered directly into the cytoplasm of the target cell [13].

iii) Acid-Induced Fusion: The fusion process of virosomes is often pH-dependent. The **acidification** of the endosomal compartment, following the uptake of virosomes by endocytosis, induces a conformational change in the viral glycoproteins. This pH-triggered fusion event allows for the fusion of the virosome with the endosomal membrane, releasing its cargo into the cytoplasm [9]. This property mimics the mechanism by which viruses enter host cells after being engulfed in endosomes.

Fusogenic Activity and Lipid Composition

i) Membrane Fluidity and Lipid Composition: The lipid composition of the virosome, including the presence of cholesterol and phospholipids, plays a crucial role in the fusion efficiency. Lipids that mimic the properties of viral membranes enhance the fusogenic activity of the virosome. Membrane fluidity is essential for efficient fusion, as it enables the virosome to integrate into the host cell membrane. The presence of certain lipids, such as **dipalmitoylphosphatidylcholine (DPPC)**

and **phosphatidylethanolamine (PE)**, can improve the membrane's fusogenic properties [12].

ii) Cholesterol: Cholesterol is an important component in both virosome and virus membrane structures. It enhances membrane stability and fluidity, making the fusion process more efficient. Cholesterol allows for optimal membrane curvature and flexibility, which are required for the fusion of the virosome with the target cell membrane [9].

Specificity of Fusion

Target Cell Specificity: One of the distinctive features of virosomes is their ability to fuse specifically with certain types of cells. This is determined by the viral glycoproteins incorporated into the virosomes, which are designed to recognize specific cell surface receptors. For example, virosomes that incorporate **hemagglutinin** from the influenza virus can specifically target cells expressing **sialicacid** receptors on their surface. This receptor-mediated fusion ensures that virosomes deliver their payload directly to the intended target cells [9].

Safety Profile in Fusion

No Genetic Material:Unlike viral vectors, virosomes do not contain viral genetic material. As a result, although virosomes exhibit fusogenic activity, they do not replicate within host cells, reducing the risks of viral infections or oncogenesis [11]. This makes virosomes a safer alternative to traditional viral vectors for gene therapy and drug delivery, while still taking advantage of the efficient fusion properties provided by viral glycoproteins.

Fusion and Drug Delivery Efficiency

Efficient Cargo Release: The fusion characteristics of virosomes allow for highly efficient release of encapsulated therapeutic agents into the cytoplasm. After fusion with the host cell membrane, the virosome disassembles and releases its cargo, such as nucleic acids, proteins, or small molecules, directly into the target cell. This direct release into the cytoplasm ensures that the cargo is available for its intended biological activity, such as gene expression or therapeutic effects [11].

Potential for Targeted Gene and Drug Delivery

i) Gene Therapy: Virosomes' ability to fuse efficiently with host cells makes them a powerful tool for gene therapy. By incorporating viral glycoproteins like hemagglutinin, virosomes can specifically target cells in a tissue-selective manner, delivering genetic material (such as DNA or RNA) to cells for therapeutic purposes [9].

ii) Cancer Therapy: Virosomes can be engineered to deliver anticancer drugs or therapeutic genes directly to cancer cells by exploiting the receptor-mediated fusion mechanism. This approach minimizes damage to surrounding healthy tissues, enhancing the specificity and efficacy of cancer therapies [12].

Table 2: Summary of Fusion Characteristics of Virosomes

Characteristic	Description
Fusion Mechanism	Receptor-mediated fusion with host cell membrane using viral glycoproteins (e.g., hemagglutinin)
pH-Dependent Fusion	Fusion triggered by acidification in endosomal compartments
Specificity	Target cell specificity due to viral glycoprotein-receptor interactions (e.g., sialic acid recognition)
Fusogenic Activity	Enhanced by lipid composition, including cholesterol and phospholipids
Cargo Release	Efficient direct release of encapsulated therapeutic agents into the cytoplasm
Safety	Non-replicative, reducing risks of viral infection or genetic modification

Virosomes and its preclinical and clinical application in cancer therapy

Virosomes have emerged as a promising tool in cancer therapy due to their ability to efficiently deliver therapeutic agents such as chemotherapeutic drugs, nucleic acids, and immunotherapeutic proteins directly to cancer cells. The unique

properties of virosomes, such as their ability to mimic viral infections, receptor-mediated cell entry, and safe drug delivery capabilities, make them a powerful candidate for both preclinical and clinical applications in cancer treatment. Here, we discuss the potential of virosomes in cancer therapy, including their preclinical and clinical applications.

Mechanism of Action in Cancer Therapy

Virosomes are lipid vesicles that incorporate viral envelope proteins, such as **hemagglutinin (HA)** and **neuraminidase (NA)**, which enable them to fuse with the cell membrane of target cells. This fusion mechanism is receptor-mediated, and the viral glycoproteins allow virosomes to specifically target cells that express the corresponding receptors on their surface. Once the virosomes fuse with the target cells, they deliver their cargo, which can include:

- **Chemotherapeutic agents**: Drugs like paclitaxel, doxorubicin, or cisplatin.
- **Nucleic acids**: Such as DNA, RNA, or siRNA for gene therapy or RNA interference (RNAi).
- **Immunotherapeutic agents**: Such as tumor antigens or cytokines to trigger immune responses against cancer cells.

The targeted delivery of these agents enhances their therapeutic efficacy while minimizing off-target effects, which is a significant advantage over conventional drug delivery systems [9].

Preclinical Applications in Cancer Therapy

Targeted Drug Delivery

Virosomes have been shown to deliver chemotherapeutic agents specifically to tumor cells. Studies have demonstrated that virosomes can enhance the intracellular uptake of drugs, leading to improved therapeutic outcomes in preclinical models. For example, virosomes have been used to encapsulate and deliver **paclitaxel** and **doxorubicin** to cancer cells. These virosomes specifically target cells overexpressing certain receptors such as **epidermalgrowth factor receptor (EGFR)** or **sialic acid**-containing receptors found on many cancer cells [11].

Gene Therapy

Virosomes can also be used in gene therapy for cancer treatment by delivering therapeutic genes directly into cancer cells. Nucleic acids, such as **p53 tumor suppressor genes**, or **antisense oligonucleotides**, can be encapsulated within virosomes. These virosomes facilitate the transfer of genetic material to cancer cells, where the gene product can suppress tumor growth or enhance the cytotoxicity of chemotherapeutic drugs [9].

Immune Activation

Virosomes can stimulate immune responses by incorporating tumor-associated antigens (TAAs) or by carrying immune modulators such as **interleukin-2 (IL-2)**. This strategy has been tested in preclinical cancer models where virosomes carrying tumor antigens induced both humoral and cellular immune responses. By targeting the immune system, virosomes may enhance the body's natural ability to recognize and destroy tumor cells [12].

Co-delivery of Combination Therapies

Another promising preclinical approach is the use of virosomes for the **co-delivery of combination therapies**. This strategy involves encapsulating multiple therapeutic agents within the same virosome. For example, virosomes can deliver a combination of **chemotherapy** and **gene therapy** agents to tumor cells, potentially enhancing the therapeutic effect while overcoming drug resistance mechanisms [18].

Clinical Applications in Cancer Therapy

Clinical Trials of Virosomes in Cancer Treatment

Several studies and clinical trials have explored the potential of virosomes in cancer therapy. One of the most significant applications is in the development of **cancer vaccines**. Virosomes can be used as vaccine delivery systems by encapsulating tumor antigens. Clinical trials have tested virosomes that deliver **tumor-associated antigens** (TAAs) such as **HER2/neu** and **MART-1**, which are overexpressed in certain types of cancer. These virosome-based vaccines have been shown to induce tumor-specific immune responses in cancer patients, providing a platform for cancer immunotherapy [18].

Gene Therapy in Clinical Settings

In clinical settings, virosomes have been tested for the delivery of **gene therapy** in patients with cancer. For example, virosomes have been used to deliver **antisense oligonucleotides** that target and inhibit oncogenes such as **Bcl-2** or **Myc**, which are involved in tumor progression and survival. In addition, virosomes have been employed for the delivery of **tumor suppressor genes**, such as **p53**, to restore normal cell cycle regulation and induce apoptosis in tumor cells [17].

Tumor-Specific Targeting

Clinical studies have demonstrated that virosomes can efficiently target tumors in humans. For example, virosomes incorporating **influenza virus hemagglutinin** proteins have been shown to specifically bind to **sialic acid** receptors overexpressed on the surface of tumor cells. By using this targeting mechanism, virosomes can deliver chemotherapy agents and immunotherapeutics directly to the tumor, increasing drug concentration at the site of the cancer and reducing systemic toxicity [11].

Combination of Chemotherapy and Immunotherapy

In clinical settings, virosomes are also being tested for the combination of **chemotherapy** and **immunotherapy**. For instance, virosomes can deliver a chemotherapeutic agent and an immune modulator, such as **interferon**, within the same vesicle. This approach has the potential to not only kill tumor cells directly but also activate the immune system to recognize and target residual cancer cells, reducing the likelihood of tumor recurrence [16].

Challenges and Future Directions

While virosomes offer a promising approach for cancer therapy, several challenges remain:

i) ***Scalability and Manufacturing***: The production of virosomes for clinical use is complex, and scaling up the production process remains a significant challenge. Ensuring consistent quality, reproducibility, and large-scale production of virosomes is crucial for their successful transition to widespread clinical use.

ii) ***Targeting Efficiency***: Although virosomes can be engineered to target specific cancer cells, optimizing the targeting specificity and

minimizing off-target effects are critical for improving therapeutic outcomes and reducing toxicity to healthy tissues.

iii) ***Regulatory Approval***: As virosomes are considered a novel drug delivery system, regulatory approval for clinical use requires extensive safety and efficacy data, including long-term follow-up to evaluate potential side effects.

Virosomes represent a powerful tool for targeted cancer therapy, offering several advantages over traditional drug delivery systems. They enable efficient, receptor-mediated targeting of cancer cells and can deliver a variety of therapeutic agents, including chemotherapeutics, nucleic acids, and immunotherapies. While virosome-based therapies have shown promising results in preclinical models, their clinical applications are still evolving. Ongoing clinical trials and advancements in virosome design

Approaches to virosome targeted drug delivery (VTDD)

Virosome-targeted drug delivery (VTDD) is a promising therapeutic strategy that uses virosomes to deliver bioactive agents to specific target cells, often for applications in gene therapy, cancer treatment, and vaccine development. By incorporating viral glycoproteins into lipid vesicles, virosomes combine the advantages of both viral vectors and liposomes, offering efficient delivery and specific targeting while minimizing the risks associated with viral-based systems. The following outlines the current approaches to enhancing VTDD.

Receptor-Mediated Targeting

i) Glycoprotein Incorporation: Virosomes are constructed by embedding viral glycoproteins (e.g., hemagglutinin (HA), neuraminidase (NA)) into the lipid bilayer. These glycoproteins recognize and bind to specific receptors on target cell surfaces, facilitating cell-specific uptake through receptor-mediated endocytosis. This targeting mechanism ensures that the virosome delivers its payload to the desired cells, minimizing off-target effects [11].

ii) Engineering for Specific Receptors: The specificity of virosome targeting can be further enhanced by modifying the viral glycoproteins or lipid composition to recognize unique markers expressed on the surface of cancer cells, immune cells, or other disease-related tissues. For instance, targeting overexpressed receptors like

EGFR (epidermal growth factor receptor) in cancer cells has shown promising results in targeted drug delivery and cancer immunotherapy [9].

Surface Modification for Enhanced Targeting

i) Ligand Conjugation: One of the most effective ways to improve the specificity of virosomes is by conjugating ligands (e.g., antibodies, peptides, or small molecules) to the virosomal surface. These ligands can specifically bind to receptors overexpressed on target cells, such as HER2 in breast cancer or CD44 in tumor-associated cells. This method enhances the selectivity and efficiency of virosome-mediated drug delivery by ensuring that virosomes preferentially target and enter the correct cells [12].

ii) Nanobody and Peptide-Based Targeting: Another strategy involves using nanobodies or short peptides that specifically bind to target cells. Nanobodies can be engineered to recognize certain tumor antigens or pathogens, improving the targeting and therapeutic efficacy of virosomes in a variety of clinical settings [15]

Targeting Immune Cells for Vaccine Development

i) Immune Modulation and Antigen Delivery: Virosomes are widely used in the development of vaccines because of their ability to stimulate the immune system in a manner similar to that of natural viral infections. By incorporating viral proteins or antigens into the virosomal structure, these systems can enhance both humoral and cellular immune responses. For example, the influenza virus-derived virosomes, which incorporate hemagglutinin (HA) and neuraminidase (NA), have been utilized to deliver influenza antigens and enhance immunity against the virus [11].

ii) Cancer Vaccination: Virosomes are also being explored for cancer immunotherapy. Cancer cell-derived antigens can be incorporated into the virosomes, allowing for direct targeting to the tumor and activation of immune cells to generate an antitumor response. Recent studies have demonstrated that virosome-based cancer vaccines can stimulate both T cell-mediated and antibody-mediated immunity against tumor cells [18].

Targeting Specific Organs or Tissues

i) Liver-Specific Targeting: Virosomes can be engineered to target specific organs, such as the liver, for the delivery of gene therapy or drugs for hepatic diseases. By

incorporating ligands that specifically bind to liver receptors like asialoglycoprotein receptors (ASGPR), virosomes can efficiently deliver therapeutic agents, such as RNA-based drugs or hepatotropic proteins, to liver cells. This approach has significant potential for treating liver diseases, including hepatitis and liver cancer [9].

ii) Brain-Specific Delivery: Targeting the blood-brain barrier (BBB) for drug delivery remains a significant challenge in neurology. Recent advancements have explored using virosomes to deliver therapeutics across the BBB. By attaching ligands that recognize transferrin receptors (TfR) or other BBB-specific receptors to the surface of virosomes, researchers have been able to facilitate more efficient drug delivery to the brain for diseases like Alzheimer's and Parkinson's [17].

Combination with Other Delivery Systems

i) Polymer-based and Liposome-based Combination: Virosomes are often combined with other advanced drug delivery systems, such as liposomes or polymeric nanoparticles, to enhance their stability, loading capacity, and release profiles. This combination can increase the payload delivered to the target site while ensuring controlled release over extended periods [12].

ii) Stimuli-Responsive Systems: Recent research has integrated virosomes with stimuli-responsive systems, such as pH-sensitive materials or light-sensitive compounds. These hybrid systems can enable controlled release of therapeutic agents upon exposure to specific environmental cues at the target site, improving the efficiency of treatment [16].

Multifunctional Virosomes for Multi-Target Delivery

Simultaneous Targeting: Advanced virosome formulations are being developed to target multiple receptors or deliver multiple therapeutic agents simultaneously. By modifying the surface of the virosomes with various ligands or encapsulating different types of drugs, it is possible to address multifaceted diseases like cancer, where both gene therapy and chemotherapy are required. These multifunctional virosomes hold promise for more comprehensive and effective treatment strategies [18].

Future Prospects in Virosome-Based Targeted Drug Delivery (VTDD)

Virosomes have emerged as promising carriers for targeted drug delivery, offering several advantages over traditional drug delivery systems, such as enhanced targeting efficiency, reduced side effects, and improved therapeutic outcomes. The future of Virosome-based Targeted Drug Delivery (VTDD) holds significant potential, with several advancements on the horizon that could further refine their applications in cancer therapy, gene therapy, immunotherapy, and other fields. The continued development of virosome technology could revolutionize the way diseases, especially cancer, are treated, by enabling more precise, effective, and safe therapeutic strategies. Here, we explore the key future prospects of VTDD.

i) ***Engineering Virosomes for Enhanced Specificity and Targeting***

One of the primary challenges in VTDD is optimizing the specificity and efficiency of virosomes for targeted delivery. Future advancements will focus on **engineering virosomes** to enhance their ability to specifically target cancer cells or tissues of interest. By incorporating specific ligands, such as **monoclonal antibodies (mAbs)**, **aptamers**, or **peptides**, virosomes can be designed to target particular **receptors** or **tumormarkers** that are overexpressed in cancer cells. This approach would minimize off-target effects, ensuring that the therapeutic agents are delivered exclusively to cancer cells, reducing systemic toxicity and enhancing therapeutic efficacy [12].

Additionally, the use of **nanostructuredvirosomes**, with a more controlled size and shape, could further optimize their ability to penetrate tumors and interact with target cells. Innovations in **surfacemodification** and **functionalization** will enhance their targeting precision and their ability to overcome biological barriers like the blood-brain barrier (BBB), which is a critical limitation for the treatment of brain cancers [18].

ii) ***Integration with Nanotechnology***

The integration of **nanotechnology** with virosomes holds immense potential for improving their drug delivery capabilities. By incorporating **nanoparticles** or **nano-carriers** into virosome formulations, it may be possible to further enhance their

biocompatibility, **stability**, and **drugencapsulationefficiency**. For example, the combination of virosomes with **gold nanoparticles** or **polymeric nanocarriers** could provide additional **drug release control**, protect against premature drug degradation, and allow for more efficient drug encapsulation [9].

Furthermore, the use of **multifunctional virosomes** that incorporate both therapeutic agents and imaging agents (e.g., **fluorescent dyes** or **magnetic nanoparticles**) will allow for **real-timemonitoring** of drug delivery, facilitating better assessment of treatment response and providing valuable diagnostic information [11].

iii) ***Personalized Medicine and Precision Therapy***

With the growing emphasis on **personalizedmedicine**, VTDD could play a pivotal role in tailoring treatments to individual patients based on their unique genetic makeup and disease characteristics. By incorporating specific **tumor markers** or **biomarkers** into the design of virosomes, treatments could be customized to target the molecular profile of each patient's tumor. This could lead to more effective therapies and reduce unnecessary side effects associated with non-targeted treatments.

The use of **genomic** and **proteomic** data to design personalized virosome-based therapies is likely to be a key area of development in the coming years. For instance, **targeting specific mutations** or altered signaling pathways within cancer cells could enhance the precision of drug delivery and increase the likelihood of successful treatment outcomes [16].

iv) ***Overcoming Biological Barriers***

One of the challenges in targeted drug delivery is overcoming biological barriers, such as **cellularmembranes**, **endosomal entrapment**, and the **blood-brain barrier (BBB)**. The future of VTDD will likely see significant advances in improving the **penetration** of virosomes across these barriers. Strategies such as **pH-sensitive virosomes**, which can release their cargo in acidic environments (such as those found in tumors or endosomes), will be further optimized. Additionally, virosomes

could be engineered to evade **immune system recognition**, prolonging their circulation time and improving drug delivery efficiency [18].

Research into virosomes that can cross the **blood-brain barrier** (BBB) holds particular promise for treating **central nervous system (CNS) disorders**, including **brain tumors**. Innovations such as incorporating **transport peptides** or **nanoparticles** that can facilitate BBB penetration will be crucial in expanding the applications of virosomes to neurological diseases [9].

*v) **Immunotherapy and Cancer Vaccines***

Virosomes are already being explored for use in **cancer vaccines** and **immunotherapy**, particularly due to their ability to enhance immune responses. The future of VTDD will likely see virosomes being further developed to deliver **tumor antigens** or **immune-modulating agents** to trigger and enhance immune responses against tumors. Virosome-based cancer vaccines have shown the potential to induce both **humoral** and **cellular immune responses**, leading to targeted killing of cancer cells and prevention of tumor recurrence [12].

Future efforts will focus on **combining virosomes with immune checkpoint inhibitors** (e.g., **PD-1/PD-L1 inhibitors**) to create **combination therapies** that enhance both the immune response and direct cytotoxic effects on cancer cells. This synergistic approach could lead to more effective treatment strategies and overcome resistance to traditional cancer therapies [11].

*vi) **Scaling up Production and Regulatory Challenges***

While the potential of virosomes in drug delivery is immense, the **scalability of production** remains a significant challenge. The manufacturing of virosomes for clinical applications must be optimized to ensure high yields, reproducibility, and cost-effectiveness. Advances in **biotechnology** and **automatedproduction systems** will likely address these issues and facilitate large-scale virosome production for commercial use.

Additionally, **regulatory hurdles** related to the safety and efficacy of virosome-based drug delivery systems need to be navigated carefully. As virosomes are a novel delivery platform, regulatory authorities may require comprehensive

preclinical and **clinical safety data** before they can be approved for widespread clinical use. Collaborative efforts between researchers, pharmaceutical companies, and regulatory bodies will be crucial to overcome these challenges [18].

The future of Virosome-Based Targeted Drug Delivery (VTDD) holds tremendous promise, with the potential to revolutionize the treatment of cancer and other diseases. With advancements in virosome engineering, nanotechnology integration, personalized medicine, and overcoming biological barriers, VTDD could become a key player in targeted and precision therapies. Continued research and development are essential to addressing the challenges related to manufacturing, regulatory approval, and therapeutic efficacy, paving the way for broader clinical applications in the near future.

Table 3: First generation virosomes

Products	Indication	Vaccine composition
Epaxal ®	Hepatitis A Adult	A(H1N1) virosomes & inactivated Hepatitis A virus
Inflexal ®	Seasonal Influenza All age groups	Virosomes from 3 Influenza strains A(H1N1), A(H3N3), B
Nasalflu®	Seasonal Influenza Intranasal application	Virosomes from 3 Influenza strains A(H1N1), A(H3N2), B & HLT adjuvant
Invivac ®	Seasonal Influenza	Virosomes from 3 Influenza strains A(H1N1), A(H3N2)B

Epaxal ® Junior	Hepatitis A Child	A(H1N1) virosomes & inactivated Hepatitis A virus

Table 4: Second generation Virosomes

Disease, target, effector	Antigen configuration	Administration Route
HIV Gp4 1Antibody	1 Peptide membrane-anchored	Intramuscular prime intranasal boost
Malaria Plasmodiumfalciparum AMA-1 & CSPantibody	2 peptides membrane-anchored	Intramuscular
Breast cancer Her2/neuAntibody	3 peptides membrane-anchored	Intramuscular

Table 5: Marketed Products of Virosomal drug delivery

S. No.	Virosomal preparations	Application
A	Virosomes antigen based products	
1	1 Hepatitis A virus envelope proteins (EpaxalW)	Hepatitis a
2	Influenza virus (InflexalW V)	Influenza
B	Virosomal antigen preparations under clinical trials	
1	Diphtheria/tetanus toxoid virus envelope proteins	Diphtheria, Tetanus

		Malaria
2	Loop I Peptidomimetic from III domain of Plasmodium falciparum AMA-1	
3	PEV6	Breast cancer
	Virosomal antigen preparations under pre-clinical trials	
C		
1	Doxorubicin	Cancer
2	Doxorubicin	Ovarian carcinoma
3	L-myc antisense ODNs	Cancer
4	DNA-encoded TAA Prostate	Carcinoma
5	DNA-encoded mumps antigen	Mumps

Table 6: Virosomal drug delivery some US Patents

S.No.	US Patent No.	Title
1	7576066	Nucleic acid compositions for stimulating immune responses
2	7615227	Use of CpG oligodeoxynucleotides to induce angiogenesis

3	7615377	Fluorescein-based metal sensors
4	7615539	Nucleic acid-lipophilic conjugates
5	7618641	Functionally reconstituted viral membranes containing adjuvant

Conclusion

Virosome-targeted drug delivery holds significant promise for personalized medicine. By tailoring the virosome formulations to the individual's specific disease markers, it is possible to develop highly customized therapies that maximize efficacy and minimize side effects [15].

Despite their promise, the large-scale production of virosomes remains challenging due to the complexity of their formulation. Overcoming this hurdle is crucial for translating virosome-based drug delivery systems into clinical and commercial applications [12].

Virosomes represent a versatile and promising approach for targeted drug delivery, offering high specificity and efficiency in a range of therapeutic applications. By incorporating viral glycoproteins and modifying their surface properties, virosomes can be designed for precise targeting, making them valuable tools in gene therapy, vaccine development, and cancer treatment. As technology progresses, the integration of virosomes with other drug delivery systems and the development of multifunctional virosomes will expand their therapeutic potential.

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