Template/Pro forma for Submission

NMHS-Himalayan Institutional Project Grant

NMHS-FINAL TECHNICAL REPORT (FTR)

NMHS Reference No.:	**GBPI/NMHS-2017-18/HSF-02**

Date of Submission:	2	8	0	3	2	0	2	2
	d	**d**	**m**	**m**	**y**	**y**	**y**	**y**

NATIONAL MISSION ON HIMALAYAN STUDIES (NMHS)

Himalayan Research Fellowship Proposal- Year 2017-18

Sanctioned Fellowship Duration: *from* (**28.03.2018**) *to* (**31.12.2021**).

Extended fellowship duration: *from* (**01.01.2022**) *to* (**30.12.2022**).

***Submitted to*:**
Er. Kireet Kumar
Scientist 'G' and Nodal Officer, NMHS-PMU
National Mission on Himalayan Studies, GBP NIHE HQs
Ministry of Environment, Forest & Climate Change (MoEF&CC), New Delhi
E-mail: nmhspmu2016@gmail.com; kireet@gbpihed.nic.in; kodali.rk@gov.in

***Submitted by*:**
[*Dr USN Murty*
Director, NIPERG]
[*Contact No.: 9127060998*]
[*E-mail: murtyusn@gmail.com*]

GENERAL INSTRUCTIONS:

1. The Final Technical Report (FTR) has to be commenced from the date of start of the Institutional Fellowship (as per the Sanction Order issued at the start of the Fellowship) till its completion. Each detail has to comply with the NMHS Sanction Order.
2. The FTR should be neatly typed (in Arial with font size 11 with 1.5 spacing between the lines) with all details as per the enclosed format for direct reproduction by photo-offset process. Colored Photographs (4-5 good action photographs), tables and graphs should be accommodated within the report or should be annexed with captions. Sketches and diagrammatic illustrations may also be given giving step-by-step details about the methodology followed in technology development/modulation, transfer and training. Any correction or rewriting should be avoided. Please give information under each head in serial order.
3. Training/ Capacity Building Manuals (with detailed contents of training programme, technical details and techniques involved) or any such display material related to fellowship activities along with slides, charts, photographs should be sent at the NMHS-PMU, GBP NIHE HQs, Kosi-Katarmal, Almora 263643, Uttarakhand. In all Knowledge Products, the Grant/ Fund support of the NMHS should be duly acknowledged.
4. The FTR Format is in sync with many other essential requirements and norms desired by the Govt. of India time-to-time, so each section of the NMHS-FTR needs to duly filled by the Fellowship Coordinator/ PI and verified by the Head of the Implementing Institution/ University.
5. Five (5) bound hard copies of the NMHS-Institutional Fellowship Final Technical Report (FTR) and a soft copy should be submitted to the **Nodal Officer, NMHS-PMU, GBP NIHE HQs, Kosi-Katarmal, Almora, Uttarakhand** *via* e-mail nmhspmu2016@gmail.com.

The FTR is to be submitted into following two parts:

Part A – Cumulative Fellowship Summary Report

Part B – Comprehensive Report

Following Financial and other necessary documents/certificates need to be submitted duly signed and verified along with Final Technical Report (FTR):

Annexure I	Consolidated and Audited Utilization Certificate (UC) & Statement of Expenditure (SE), including interest earned for the last Fiscal year including the duly filled GFR-19A (with year-wise break-up)
Annexure II	Consolidated Interest Earned Certificate
Annexure III	Consolidated Manpower Certificate and Direct Benefit Transfer (DBT) Details showing the education background, i.e. NET/GATE etc. qualified or not, Date of joining and leaving, Salary paid per month and per annum (with break up as per the Sanction Order and year-wise).
Annexure IV	Details and Declaration of Refund of Any Unspent Balance as Real-Time Gross System (RTGS) in favor of NMHS GIA General
Annexure V	Details of Technology Transfer and Intellectual Property Rights developed.

DSL: Date of Sanction Letter

2	8	0	3	**2**	**0**	**1**	**8**
d	d	m	m	y	y	y	y

DPC: Date of Project Completion

3	1	1	2	**2**	**0**	**2**	**2**
d	d	m	m	y	y	y	y

Part A: CUMULATIVE SUMMARY REPORT

(to be submitted by the Coordinating Institute/Coordinator)

1. Details ~~Associateship/~~Fellowships

1.1 Contact Details of Institution/University

NMHS Fellowship Grant ID/ Ref. No.:	**GBPI/NMHS-2017-18/HSF-02**
Name of the Institution/ University:	NIPER-GUWAHATI
Name of the Coordinating PI:	Dr. USN Murty, Director, NIPER-Guwahati
Point of Contacts (Contact Details, Ph. No., E-mail):	9127060998, murtyusn@gmail.com

1.2 Research Title and Area Details

i.	Institutional Fellowship Title:	NATIONAL MISSION ON HIMALAYAN STUDIES (NMHS) Himalayan Research Fellowship Proposal- Year 2017-18					
ii.	IHR State(s) in which Fellowship was implemented:	Assam					
iv.	Scale of Fellowship Operation	Local:		Regional: North East		Pan-Himalayan:	
iii.	Study Sites covered (*site/location maps to be attached*)	Himalayan rural areas from Assam, Meghalaya, Manipur, Tripura, Arunachal Pradesh					
v.	Total Budget Outlay (Crore) :	INR 1.44 Cr. (GBPI/NMHS-2017-18/HSF-02 & GBPNI/NMHS-2017-18/HSF-02/599/231/288/413					

1.3 Details Himalayan Research /Project Associates/Fellows inducted

Type of Fellowship	Nos.	Work Duration	
		From	To
Research Associates	02	04.06.2018	31.10.2019
		06.12.2019	2021
		01.06.2018	30.11.2019
		20.01.2020	23.12.2020

Sr. Research Fellow	00		
Jr. Research Fellows	05	30.07.2018	Till date
Project Fellows	00		

2. Research Outcomes

2.1. Abstract (not more than 1000 words) [it should include background of the study, aim, objectives, methodology, approach, results, conclusion and recommendations based on the institutional fellowship proposal sanctioned under the NMHS).

Background: The North-East region of India contains more than one-third of the country's total biodiversity. The area represents an integral part of Indo Myanmar's biodiversity hotspot, one of 25 global biodiversity hotspots recognized. The eastern Himalayan region support one of the world's richest alpine floras with a high level of endemism (WWF and ICIMOD 2001); (www, biodiversityhotspots.org), Northeast India has India's richest reservoir of plant diversity and supports around 50% of India's total plant diversity (Mao & Hynniewta, 2000). The medicinal plants constitute an essential bio-resource of Northeast India, many of which are used by various ethnic groups for their primary healthcare needs. ***Objectives/ Aim:*** Most populations, especially in rural areas & different ethnic communities, depend on the oral knowledge of the Traditional Health Practices (THPs), remedies, and therapies to meet their primary health needs.

Methodology's: The lack of a detailed database of medicinal plants, their availability, and claimed pharmacological benefits is a challenge hindering the prospects of these traditional systems of medicine in the Himalayan belt. In this regard, a database containing a list of medicinal plants available in the Himalayan belt of the Northeast region will be highly beneficial for the modern phyto/pharmaceutical industry.

Approach: The next step involves exploring the new traditional knowledge systems; an initial screen can help isolate the medically significant properties of plants. The Pharmacological properties and simultaneous analytical characterization of bioactive molecules from the unexplored traditional knowledge systems, and their scientific validation of efficacy, safety, and dosage could be of potential value for modern health research.

***Results*:** Further, taking the medicinal plants' research outcomes to the Himalayan inhabitants for their rational use creates awareness and sensitization of their importance. This will aid in the cultivation, conservation, and commercial utility of medicinal plants among the traditional healers & local people of the Northeast region. **Conclusion:** Considering the above-said points, we have framed the following aim & objectives of the project.

Recommendations: Further toxicity and safety studies are required for the data generated from the current project to translate the use of these medicinal plants of the Himalayan region from North-East states to use them as nutraceuticals or adjuvant therapy for the treatment of oxidative stress mediated diseases.

2.2. Objective-wise Major Achievements

S. No.	Cumulative Objectives	Major achievements (in bullets points)
HRA001 (Dr. Sahabuddin Ahmed)	Database development on Himalayan Indigenous Knowledge Systems (IKS) prevailing in NE Hills	Collected the information of around 300 medicinal plants grown in Himalayan region and developed the consolidated database. Development of Digital Library on the above consolidated data is under progress. Also explored the pharmacological activities of bioactive components (Andrographolide, 7,8-Dihydroxyflavone, Hesperidin) of the medicinal plants grown in Himalayan region of their neuroprotective activity employing *in vitro* and *in vivo* models. Published three papers in international peer reviewed journals. (Detail report enclosed as Annexure 1)
HRA002 (Dr Deepak Bharadwaj)	Validation and valuing of >5 selected traditional, ecological knowledge and practices	Prepared database on Traditional formulations used by around 70 number of traditional healers of Northeast Region. Based on traditional usage three traditional healers' formulations (*TMH-2*, *TMC-3* and *TMH-11*) and extracts of Dillenia Indica and *Dillenia pentagyna* were selected for testing anti-malarial activity in in vitro and in vivo models. All the three formulations and extracts showed potent activity against plasmodium falcifarum in in vitro models. However, efficacy is not as expected in the in vivo mice model. Further formulation studies are required to translate these formulations and extracts in the form of products. Published two papers in international peer reviewed journals and two book chapters. (Detail report enclosed as Annexure 2)

HJRF001 (Ms.Siddi Jain)	Pharmacological activities, efficacy, safety and dosage evaluation of bioactive compound in potential species.	Collected, authenticated, extracted and evaluated for biological efficacy of the extracts from the following medicinal plants of *Zanthoxylum armatum (ZA), Elsholtzia communis (EC) and Garcinia pedunculata (GP)*. Alcoholic and hydroalcoholic extracts of above plants showed good antioxidant and organo protective activity against doxorubicin and cisplatin induced cardio and nephrotoxicity respectively. Further suitable dosage form development is warranted to translate their use as nutraceuticals or herbal medicines. Published one papers in international peer reviewed journals. (Detail report enclosed as Annexure 3
HJRF002 (Mr. Shantanu P.A)	Pharmacological activities, efficacy, safety and dosage evaluation of bioactive compound in potential species.	Explored the pharmacological evaluation of alcoholic extracts of *Dillenia Indica and Dillenia pentagyna* as adjuvant therapy to prevent the drug induced toxicity and found good protection against cancer chemotherapeutic drugs induced organ toxicity. Also evaluated the efficacy of bioactive compounds Hispolon and evodamine against RANKL induced osteoclastogensis and MPTP induced Parkinson's disease. Published three papers in international peer reviewed journals. (Detail report enclosed as Annexure 4

HJRF003 (Dr.Datta Pawde)	Sensitisation and awareness about medicinal plant among Himalayan in habitants for their rational use	Awareness programmes on use and conservation of medicinal plants has been conducted in the villages of Assam, Meghalaya, Arunachal Pradesh, Manipur ad Tripura state Developed analytical HPLC method for simultaneous estimation of selected two drugs We have developed a novel nanoformulations for the treatment of rheumatoid arthritis Visited State Herbal Garden, Kangla Fort, Imphal West, Manipur Abstract entitled “Systematic Development of Janus Nanosized Emulsions by Quality by Design (QbD) Approach” selected and delivered a short talk in ICANN2019 held at IIT Guwahati campus during December 18-21, 2019 Visited Kaziranga National Orchid and Biodiversity Park, Kaziranga, Assam Visited Nameri National Park and Forest Reserve, Assam Two book chapter has been published Presented poster at Virtual DDG India meeting 2020 Participated in ‘International webinar on Quality by Design (QbD)-Industrial Approach’ Participated in ‘Entrepreneurship Development Seminar series for Pharma Sector, Part-I’ (Detail report enclosed as Annexure 5)
HJRF004 (Dr.Vishal Chaudhary)	Identification and collection and quantification of 5 most endangered plants with medicinal potential in region	NIPER-G conducted field survey in different Himalayan rural areas from Assam, Meghalaya, Manipur, Tripura, Arunachal Pradesh and collected *Nepenthes khasiana, Coptis teeta, Shorea assamica, Aquilaria malaccensis, Vanilla planifolia* IUCN Red listed Medicinal plants. Also developed nanoformulation for quercetin and piperine for the effective delivery to cancer cells. (Detail report enclosed as Annexure 6)

HJRF005 (Ms.Aishwarya)	Extraction, isolation, purification, characterisation of bioactive compounds from 3 unexplored species	Extraction and phytochemical characterisation of *Dillinea India, Dillenia Pentagyna and Mesua assamica* were performed by using LCMS HRMS. Published three papers in international peer reviewed journals. (Detail report enclosed as Annexure 7)

2.3. Outputs in terms of Quantifiable Deliverables*

S. No.	Quantifiable Deliverables*	Monitoring Indicators*	Quantified Output/ Outcome achieved	Deviations made, if any, & Reason thereof:
HRA001 (Dr. Sahabuddin Ahmed)	Database development on Himalayan Indigenous Knowledge Systems (IKS) prevailing in NE Hills	Collected the information of around 300 medicinal plants grown in Himalayan region and developed the consolidated database. Development of Digital Library on the above consolidated data is under progress. Also explored the pharmacological activities of bioactive components (**Andrographolide, 7,8-Dihydroxyflavone,**	Published three papers in international peer reviewed journals. (Detail report enclosed as **Annexure 1**)	NA

		Hesperidin) of the medicinal plants grown in Himalayan region of their neuroprotective activity *in vitro* and *in vivo* models.		
HRA002 (Dr. Deepak Bharadwaj)	Validation and valuing of >5 selected traditional, ecological knowledge and practices	Prepared database on Traditional formulations used by around 70 number of traditional healers of Northeast Region. Based on traditional usage three traditional healers' formulations (TMH-2, TMC-3 and TMH-11) and extracts of *Dillenia Indica and Dillenia pentagyna* were selected for testing anti-malarial activity in *in vitro* and *in vivo* models. All the three formulations and extracts showed potent activity against plasmodium falcifarum in in vitro	Published two papers in international peer reviewed journals and two book chapters. (Detail report enclosed as **Annexure 2**)	NA

		models. However, efficacy is not as expected in the *in vivo* mice model. Further formulation studies are required to translate these formulations and extracts in the form of products.		
HJRF001 (Ms.Siddi Jain)	Pharmacological activities, efficacy, safety and dosage evaluation of bioactive compound in potential species.	Collected, authenticated, extracted and evaluated for biological efficacy of the extracts from the following medicinal plants of *Zanthoxylum armatum (ZA), Elsholtzia communis (EC) and Garcinia pedunculata (GP).* Alcoholic and hydroalcoholic extracts of above plants showed good antioxidant and organo protective activity against doxorubicin and cisplatin induced cardio and nephrotoxicity	Published one papers in international peer reviewed journals. (Detail report enclosed as **Annexure 3**	NA

		respectively. Further suitable dosage form development is warranted to translate their use as nutraceuticals or herbal medicines.		
HJRF002 (Shantanu)	Pharmacological activities, efficacy, safety and dosage evaluation of bioactive compound in potential species.	Explored the pharmacological evaluation of alcoholic extracts of *Dillenia Indica and Dillenia pentagyna* as adjuvant therapy to prevent the drug induced toxicity and found good protection against cancer chemotherapeutic drugs induced organ toxicity. Also evaluated the efficacy of bioactive compounds Hipolon and evodamine against RANKL induced osteoclastogensis and MPTP induced Parkinson's disease.	Published three papers in international peer reviewed journals. (Detail report enclosed as **Annexure 4**	NA

HJRF003 (Dr. Datta Pawde) (Shantanu)	Sensitisation and awareness about medicinal plant among Himalayan in habitants for their rational use	Meghalaya, Arunachal Pradesh, Manipur ad Tripura state Developed analytical HPLC method for simultaneous estimation of selected two drugs We have developed a novel nanoformulations for the treatment of rheumatoid arthritis Visited State Herbal Garden, Kangla Fort, Imphal West, Manipur	**Two book chapter has been published** Presented poster at Virtual DDG India meeting 2020 Participated in 'International webinar on Quality by Design (QbD)-Industrial Approach' Participated in 'Entrepreneurship Development Seminar series for Pharma Sector, Part-I' (Detail report enclosed as **Annexure 5)**	NA
HJRF004 (Dr Vishal Chaudhary)	Identification and collection and quantification of 5 most endangered plants with medicinal potential in region	NIPER-G conducted field survey in different Himalayan rural areas from Assam, Meghalaya, Manipur, Tripura, Arunachal Pradesh and collected *Nepenthes khasiana, Coptis teeta, Shorea assamica, Aquilaria*	Also developed nanoformulation for quercetin and piperine for the effective delivery to cancer cells. (Detail report enclosed as **Annexure 6)**	NA

		malaccensis, Vanilla planifolia IUCN Red listed Medicinal plants.		
HJRF005 (Aishwarya)	Extraction, isolation, purification, characterisation of bioactive compounds from 3 unexplored species	Extraction and phytochemical characterisation of *Dillinea India, Dillenia Pentagyna and Mesua assamica* were performed by using LCMS HRMS.	Published three papers in international peer reviewed journals. (Detail report enclosed as **Annexure 7)**	NA

(*) As stated in the Sanction Letter issued by the NMHS-PMU.

2.4. Strategic Steps with respect to Outcomes (in bullets)

S. No.	Particulars	Number/ Brief Details	Remarks/ Attachment
1.	New Methodology developed		No
2.	New Models/ Process/ Strategy developed		No
3.	New Species identified		No
4.	New Database established		Yes (Attached as Annexure)
5.	New Patent, if any		Nil
	I. Filed (Indian/ International)		
	II. Granted (Indian/ International)		
	III. Technology Transfer(if any)		
6.	Others (if any)		Nil

3. Technological Intervention

S. No.	Type of Intervention	Brief Narration on the interventions	Unit Details (No. of villagers benefited / Area Developed)
1.	Development and deployment of indigenous technology	Yes	NA
2.	Diffusion of High-end Technology in the region	Yes	NA

3.	Induction of New Technology in the region	Yes	NA
4.	Publication of Technological / Process Manuals	Yes	NA
	Others (if any)		

4. New Data Generated over the Baseline Data

S. No.	New Data Details	Existing Baseline	Additionality and Utilisation New data
		Not applicable	

5. Linkages with Regional & National Priorities (SDGs, INDC, etc)/ Collaborations

S. No.	Linkages /collaborations	Details	No. of Publications/ Events Held	Beneficiaries
1.	Sustainable Development Goal (SDG)	Not applicable		
2.	Climate Change/INDC targets			
3.	International Commitments			
4.	National Policies			
5.	Others collaborations			

5.

Demonstrative Skill Development and Capacity Building/ Manpower Trained

S. No.	Type of Activities	Details with number	Activity Intended for	Participants/Trained			
				SC	**ST**	**Woman**	**Total**
1.	Workshops						
2.	On Field Trainings						
3.	Skill Development						
4.	Academic Supports	**5 JRFs and 4 RAs were trained**		**01**		**01**	**9**
	Others (if any)						

6. Financial Summary (Cumulative)*

S. No.	Financial Position/Budget Head	Funds Received	Expenditure/ Utilized	% of Total cost

I.	Salaries/Manpower cost	63,89,280.00	96,78,884.00	151
II.	Travel			
III.	Expendables &Consumables	20,10,898.00	25,91,196.00	129
IV.	Contingencies			
V.	Activities & Other Project cost			
VI.	Institutional Charges	7,58,448	7,58,448.00	100
VII.	Equipments			
	Total	91,58,626.00	1,30,28,528.00	
	Interest earned	1,56,384.00		
	Grand Total	93,15,010.00		

* Please attach the **consolidated and audited Utilization Certificate (UC)** and Year wise Statement of Expenditure (SE) separately, *ref*. **Annexure I.**

7. Quantification of Overall Research Progress

S. No.	Parameters	Total (Numeric)	Attachments* with remarks
1.	IHR State(s) Covered:	*05*	Himalayan rural areas from Assam, Meghalaya, Manipur, Tripura, Arunachal Pradesh
2.	Fellowship Site/ LTEM Plots developed:	*NA*	
3.	New Methods/ Model Developed:		
4.	New Database generated:	*01*	
5.	Types of Database generated:	*Yes for 400 Medicinal plants (Details attached as Annexure 5)*	
6.	No. of Species Collected:	*10*	
7.	New Species identified:	*0*	
8.	Scientific Manpower Developed (PhDs awarded/ JRFs/ SRFs/ RAs):	*5 JRFs and 4 RAs*	
9.	No. of SC Himalayan Researchers benefited:	*01*	*Dr Prakash Hajam*

			Currently working as postdoctoral fellow at Korean university
10.	No. of ST Himalayan Researchers benefited:	*0*	
11.	No. of Women Himalayan Researchers empowered:	*03*	*Dr Nandana Bhardwaj* *Ms. Siddi Jain* *Ms. Aishwarya Jala*
12.	No. of Knowledge Products developed:	27	
13.	No. of Workshops participated:	*01*	
14.	No. of Trainings participated:	*00*	
15.	Technical/ Training Manuals prepared:	*00*	
	Others (if any):	*NA*	

8. Knowledge Products and Publications*

S. No.	Publication/ Knowledge Products	*Number*		*Total Impact Factor*	*Remarks/* Enclosures**
		National	International		
1.	Journal Research Articles/ Special Issue (Peer-reviewed/ Google Scholar)	00	15	>50	
2.	Book Chapter(s)/ Books:	00	02		
3.	Technical Reports/ Popular Articles	00	00		
4.	Training Manual (Skill Development/ Capacity Building)	00	00		**Will be prepared under future scope of the current project**
5.	Papers presented in Conferences/ Seminars	08	00		
6.	Policy Drafts (if any)	00	00		
7.	Others (specify)				

A separate folder with the list of KPs/Publications (with impact factor) and supporting copies has been provided in the separated folder titled "Knowledge Products and Publications".

*Please append the list of KPs/ publications (with impact factor and URL link details) with due Acknowledgement to NMHS.

**Please provide supporting copies of the published documents.

9. Recommendation on Utility of Research Findings, Replicability and Exit Strategy

9.1 Utility of the Fellowship Findings

S. No.	*Research Questions Addressed*	*Succinct Answers (within 150–200 words)*
1	Database development on Himalayan Indigenous Knowledge Systems (IKS) prevailing in NE Hills	Collected the information of around 300 medicinal plants grown in the Himalayan region and developed the consolidated database. The development of a Digital Library on the above-consolidated data is required for further utilization. Also explored the pharmacological activities of bioactive components (**Andrographolide, 7,8-Dihydroxyflavone, Hesperidin**) of the medicinal plants grown in the Himalayan region of their neuroprotective activity *in vitro* and *in vivo* models.
2	Validation and valuing of >5 selected traditional, ecological knowledge and practices	Prepared database on Traditional formulations used by around 70 traditional healers of Northeast Region. Based on traditional usage three traditional healers' formulations (TMH-2, TMC-3 and TMH-11) and extracts of *Dillenia Indica and Dillenia pentagyna* were selected for testing anti-malarial activity in *in vitro* and *in vivo* models. All three formulations and extracts showed potent activity against plasmodium falcifarum in *vitro* models. However, efficacy is not as expected in the *in vivo* mice model. Further formulation studies are required to translate these formulations and extracts into the form of products.
3	Pharmacological activities, efficacy, safety and dosage evaluation of bioactive compound in potential species.	Collected, authenticated, extracted and evaluated for biological efficacy of the extracts from the following medicinal plants of *Zanthoxylum armatum (ZA), Elsholtzia communis (EC) and Garcinia pedunculata*

		(GP). Alcoholic and hydroalcoholic extracts of above plants showed good antioxidant and organo protective activity against doxorubicin and cisplatin induced cardio and nephrotoxicity respectively. **Further suitable dosage form development is warranted to translate their use as nutraceuticals or herbal medicines as per the regulatory requirements.**
4	Pharmacological activities, efficacy, safety and dosage evaluation of bioactive compound in potential species.	Explored the pharmacological evaluation of alcoholic extracts of *Dillenia Indica and Dillenia pentagyna* as adjuvant therapy to prevent the drug induced toxicity and found good protection against cancer chemotherapeutic drugs induced organ toxicity. Also evaluated the efficacy of bioactive compounds Hipolon and evodamine against RANKL induced osteoclastogensis and MPTP induced Parkinson's disease.
5	Sensitisation and awareness about medicinal plant among Himalayan in habitants for their rational use	Meghalaya, Arunachal Pradesh, Manipur ad Tripura state Developed analytical HPLC method for simultaneous estimation of selected two drugs We have developed a novel nanoformulations for the treatment of rheumatoid arthritis Visited State Herbal Garden, Kangla Fort, Imphal West, Manipur
6	Identification and collection and quantification of 5 most endangered plants with medicinal potential in region	NIPER-G conducted field survey in different Himalayan rural areas from Assam, Meghalaya, Manipur, Tripura, Arunachal Pradesh and collected *Nepenthes khasiana, Coptis teeta, Shorea assamica, Aquilaria malaccensis, Vanilla planifolia* IUCN Red listed Medicinal plants.
7	Extraction, isolation, purification, characterisation of bioactive compounds from 3 unexplored species	Extraction and phytochemical characterisation of *Dillinea India, Dillenia Pentagyna and Mesua assamica* were performed by using LCMS HRMS.

9.2 Recommendations on Replicability and Exit Strategy:

Particulars	Recommendations
Knowledge Products Replicability of Fellowship, if any	NA
Exit Strategy:	*Please describe the Exit Strategy of the fellowship, self-sustaining and benefitting the stakeholders and target communities*: Herein, we opted to phase down Exit Strategy **Phasing down:** Under this strategy, we opted for a gradual reduction of this program activities, utilizing full involvement of all recruited manpower under this project to sustain project outcomes & also to achieve the proposed research objectives.

(NMHS FELLOWSHIP COORDINATOR)

(Signed and Stamped)

(HEAD OF THE INSTITUTION)

(Signed and Stamped)

डॉ॰ यू एस एन मूर्ति / Dr. USN Murty
निदेशक / Director
राष्ट्रीय औषधीय शिक्षा एवं अनुसंधान
संस्थान (नाईपर) गुवाहाटी
National Institute of Pharmaceutical
Education & Research (NIPER) Guwahati

Place: .....
Date: ...../...../.....

PART B: COMPREHENSIVE REPORT (including all sanctioned positions of Researchers)

Based on the Fellowship Proposal submitted/approved at the time of sanction, the co-ordinating Principal Investigator shall submit a comprehensive report including report of all individual researchers.

The comprehensive report shall include an **Executive Summary** and it should have separate chapters on (1) **Introduction** (2) **Methodologies, Strategy and Approach** (3) **Key Findings and Results** (4) **Overall Achievements** (5) **Impacts of Fellowship in IHR** (6) **Exit Strategy and Sustainability** (7) **References/ Bibliography** and (8) **Acknowledgements** (It should have a mention of financial grant from the NMHS, MoEF&CC).

Further, description of Technical Activities, List of Trainings/ Workshops/ Seminars with details of trained resources, list of New Products developed under the fellowship, Manual of Standard Operating Procedures (SOPs) developed, Technology developed/Transferred etc should be enclosed as Appendix.

Report (hard copy) should be submitted to:

Er. Kireet Kumar
Scientist 'G' and Nodal Officer, NMHS-PMU
National Mission on Himalayan Studies (NMHS)
G.B. Pant National Institute of Himalayan Environment (GBP NIHE)
Kosi-Katarmal, Almora 263643, Uttarakhand

Report (soft copy) should be submitted at:

E-mail: nmhspmu2016@gmail.com; kireet@gbpihed.nic.in; kodali.rk@gov.in

PART B: COMPREHENSIVE REPORT

EXECUTIVE SUMMARY

The Executive Summary of the fellowship should not be more than 3–5 pages, covering all essential features in precise and concise manner as stated in Part A (Cumulative Fellowship Summary Report) and Part B (Comprehensive Report).

n of N *(n = Sequential number; N= Total no. of fellowships granted to the Institute/ University)*

NIPER-Guwahati under NMHS project selected almost 300 medicinal plants from different adjoining Himalayan N.E Region & prepared a Database. The Database includes parameters like Taxonomy of the plant, Vernacular name, habitat & distribution, ideal time of collection plant parts used, reported chemical constituents, reported traditional medicinal uses, their mode of administration, extraction techniques & reported Patent & marketed products. The Database preparation is mainly concentrated with to conserve this Traditional Medicinal Knowledge with a DBMS system. It is often seen that traditional knowledge is having tremendous application in drug discovery. The development of modern science and technologies notably biotechnology and information technologies have increased the value of biodiversity and associated knowledge including traditional knowledge.

Moreover, with growing evidences of active phytoconstituents within indogenous species of Northern Himalayan regions plants such as Andrographis paniculata, Primula, vulgaris, Eastern Himalaya: *antidesma bunius, Senna siamea (as seen in DBMS system)* have been found to contains important bio-active compounds composed of Andrographolide *(Andrographis paniculata), Hesperidin (Eastern Himalaya: antidesma bunius, Senna siamea), 7,8-Dihydroxyflavone (Carallia brachiata, Senna siamea)* which possess potent anti-inflammatory, antioxidant, anti-apoptotic activities in various diseases and neurological disease. Hence, we further tried to evaluate these unexplored active principles (Andrographolide, 7,8-Dihydroxyflavone, Hesperidin) in *in-vitro, in-vivo* models of Parkinson's disease, Huntington's disease, and *in-vivo* model of hesperidin against depressive-anxiety like behavior (elucidated in chronic stress and LPS mice model). Hence, we can conclude that the diverse floras within region of Himalayas are being flourished with diverse bio-actives principles which can be used in several detrimental neurological disorders and other bodily diseases.

We have initially conducted outreach, and traditional healers meet programs in India's Northeast states to meet this objective. The first traditional healers meet organized at the NIPER (Guwahati, August 2018), followed by Dhemaji Dist (Assam), Joai Dist (Meghalaya), Majuli Dist (Assam, Dec 2019), Dhemaji (Assam, Nov 2020), Jorhat (Assam, Nov 2020), Nansai Dist (Arunachal Pradesh Nov 2020) and Barpeta Dist (Assam, Nov 2020).

With these programs, we met several healers who were enthusiastic in providing their formulations to validate them scientifically for various biological claims with the state-of-art research facilities at the NIPER Guwahati. Among them, nine traditional healers have provided us with their traditional formulations to validate them against Diabetes, Malaria, and hepatoprotective properties. A confidentiality non-disclosure agreement was made between the traditional healers, and the NIPER G was created to protect the traditional knowledge. We tested three traditional formulations and two indigenous plants for the in-vitro anti-malarial efficacy and found that the alcoholic extracts from polyherbal formulations as well as medicinal plants showed good anti-malarial activity compared to the respective control groups. Further these extracts were further tested in *in vivo* efficacy studies, however these extracts have not showed good efficacy in in vivo model may be due to low bioavailability of the components in the extracts. Hence further formulation strategies are required to translate the use of these traditional knowledge for the better efficacy towards the treatment of malaria.

Approximately 50% of the new drugs introduced in the market are of natural resource. These natural resources are majorly from North-East Himalayan region***. Zanthoxylum armatum (ZA), Elsholtzia communis (EC) and Garcinia pedunculata (GP)*** were used by local people of Himalayan region as food material and also for therapeutic application as traditional use. However, there is no scientific validation about their importance as medicinal plants as well as food material. Oxidative stress (OS) is one of the principal factors mainly responsible for various ailments. Drug/disease/pollution/stress induces organ toxicity via generating enormous OS in body leading to deleterious effects. On other hand most of the herbal and pharmaceutical industries are searching for a good natural antioxidant of natural origin. As above selected natural plants are taken by local people of Himalayan region and are indicated to be safe for human use. Therefore, we want to explore the potential use of these medicinal plants as an antioxidant molecule. In order to achieve this, we have collected, authenticated, extracted these medicinal plants and found that alcoholic and hydroalcoholic extracts of ZA, EC and GP have good free radical scavenging activity when compared with reference standard like ascorbic acid. Further we also tested the effect of hydroalcoholic extracts in *in-vitro* and *in-vivo* models for their organo protective activity. We found that these extracts have shown potential protection against doxorubicin and cisplatin induced cardio and nephrotoxicity respectively in *in-vitro* and *in-vivo* model. This study highly concludes that there is a potential clinical translational of these plant extracts. Hence pre-clinical toxicity studies are required for their potential use as antioxidants in herbal industries. However further studies are also required for these medicinal plant extracts for its potential application in other diseases like inflammatory diseases, cardiovascular diseases, cancer etc.

We aim of our study is to explore efficacy of these natural extracts in various cancerous cell lines and *in-vivo* model of cancer chemotherapy induced complications. In order to explore for antioxidant properties of DI and DP, we performed a battery of antioxidant assays of various solvent extracts of DI and DP. We found hydroalcoholic fraction of DI and DP superior to standard ascorbic acid. Thus, we screened hydroalcoholic extracts of DI and DP against doxorubicin induced cardiotoxicity and cisplatin induced nephrotoxicity both in vitro and in vivo. We found the results hydroalcoholic extracts of DI and DP were very effective in attenuating the cytotoxicity caused by anticancer drugs like doxorubicin and cisplatin in cardiac (H9C2) and kidney (HEK293) cell line. In vivo study showed the treatment with hydroalcoholic extracts also reversed the biochemical, histological and functional changes induced by doxorubicin and cisplatin in cardiac and kidney parameters. Further investigation into molecular mechanism behind nephroprotective activity of DI and DP is under progress. The extracts were also evaluated for its anticancer effects where, we found that chloroform and ethyl acetate fraction possessed significant anticancer activity in oral and colon cancer cell. Further exploring for the pharmacological activities for Himalayan plants, we also screened Hispolon a bioactive compound from obtained from Phellinus linteus (endemic to Sikkim and Himachal Pradesh) for its activity against RANKL induced osteoclastogenesis *in vitro*. We found Hisplon inhibited osteoclastogenesis by downregulating NFATc1 and c-FOS expression. Thirdly, we explored for the neuroprotective effects of Evodamine a phytoconstituent isolated from Evodia rutaecarpa, and Evodia fraxinifolia H.K found in Sikkim both in in vitro and in vivo model. Overall, these studies will impart a scientific validation to these identified Himalayan plants, which will enhance conservation, commercial value and research and development in North-East region.

The objective of this study was to improve the therapeutic efficacy of chloroquine phosphate and flavopiridol in the treatment of rheumatoid arthritis (RA) by incorporating drugs into the Janus nanosized emulsion. Analytical method has been developed for simultaneous determination of chloroquine phosphate and flavopiridol in the developed nanosized emulsion. The Janus nanosized emulsion were prepared by high shear homogenization method and optimized by the Box–Behnken design (BBD). Furthermore, the therapeutic efficacy of the prepared nanosized emulsions on the adjuvant induced arthritic rats was assessed. NF-κB and iNOS expression levels was determined in rat knee joint tissue samples by real time RT-PCR.

NIPER-G conducted field survey in different Himalayan rural areas from Assam, Meghalaya, Manipur, Tripura, Arunachal Pradesh. We collected Nepenthes *khasiana, Coptis teeta, Shorea assamica, Aquilaria malaccensis, Vanilla planifolia* IUCN Red listed Medicinal plants. For collection of IUCN Red listed species we have taken proper permission from Assam State Biodiversity Board & Assam Forest Department, Kamrup Division & from CSIR-NEIST, Jorhat & prepared herbarium for proper authentification of identified species. We have also received the Accession No. of

authentification from Assam Bioresources Center, Madan Kamdev, Baihata Chariali, ASTEC, and Assam. Along with this we have also collected Mesua assamica which was previously in the IUCN Red listed Endangered category. Through proper propagation, it has been up-lifted to threatened category. Due to constraint in the collection of these endangered plants, we tested the anticancer activities for *Mesua assamica* in *in-vitro* models including cell viability assay. Whole study was performed in cancer cell lines like breast and colon cancer and found that alcoholic extract and ethyl acetate extract showed potential biological activity respectively. Further studies are going with the optimized extracts. In addition to this, we have developed nanoformulation containing bio-flavonoids as active constituents are present in these plants. Thus, nano-formulation was selected to utilize the medicinal potential of such active constituents. Thus, nanoformulation was developed and characterised for its physicochemical properties along with its in-vitro cellular evaluation against oral cancer cell line. This provides a translational form to deliver active constituents enriched nano-carriers to mitigate burden of oral cancer in the N.E. region.

North-east part of India is rich in plant biodiversity whose healing power has been realized and documented for ages. Plants from North East region of India are being widely used by local people for treatment for various diseases as well as a part of their regular diet. The scientific evidence on the biological as well as chemical properties of these plants is very limited and therefore it is important to characterize the medicinal importance of each plant. Thus, the aim of the study is extraction, isolation, purification and characterization of bioactive compounds from 3 unexplored species from North-east region of India. In this regard we have collected *Dillenia pentagyna* (NIPER/18/01), *Clerodendrum hexangularis* (NIPER/18/08), and *Dillinea indica* (NIPER/18/11) from North-east region of India due to their high availability. These plants were selected for further phytochemical investigations based on the in-house *in vitro* testing by our *HJRF-1* and *HJRF-2* on anti-oxidant and organo-protective activities. To develop chemical fingerprints of bioactive extracts LC-MS approach has been selected for rapid identification and de-replication of components. In order to identify the chemical constituents responsible for the biological activity the plant parts were dried and extracted in different solvents namely, hexane, chloroform, ethyalcetate, ethanol, and hydro-alcohol (1:1) and subjected for characterization by using analytical techniques.

Fellowship Report No.:

Researchers Details

Type of Fellowship (HRA/HJRF/HJPF)	Name of Himalayan Researcher	Date of Joining	Date of Resignation**	Research Title	Name of the PI & Designation
HRA 1	Dr.Prakash Haziram	04.06.2018	31.10.2019	Database development on Himalayan Indigenous Knowledge Systems (IKS) prevailing in NE Hills Validation and valuing of >5 selected traditional, ecological knowledge and practices	Dr. USN Murthy, Director, NIPER Guwahati
	Dr.Sahabuddin Ahmed	06.12.2019	2021		
HRA 1	Dr. Nandana Bharadwaj	01.06.2018	30.11.2019	Pharmacological activities, efficacy, safety and dosage evaluation of bioactive compound in potential species.	Dr. USN Murthy, Director, NIPER Guwahati
	Dr. Deepak Bharadwaj PVP	20.01.2020	23.12.2020	Pharmacological activities, efficacy, safety and dosage evaluation of bioactive compound in potential species.	
HJRF 1	Ms.Siddi Jain)	30.07.2018	Till date	Sensitisation and awareness about	Dr. USN Murthy, Director, NIPER Guwahati

				medicinal plant among Himalayan in habitants for their rational use	
HJRF 2	Mr. Shantanu P.A	30.07.2018	Till date	Identification and collection and quantification of 5 most endangered plants with medicinal potential in region	Dr. USN Murthy, Director, NIPER Guwahati
HJRF 3	Dr.Datta Pawde)	30.07.2018	Till date	Extraction, isolation, purification, characterisation of bioactive compounds from 3 unexplored species	Dr. USN Murthy, Director, NIPER Guwahati
HJRF 4	Dr.Vishal Chaudhary	30.07.2018	Till date	Database development on Himalayan Indigenous Knowledge Systems (IKS) prevailing in NE Hills	Dr. USN Murthy, Director, NIPER Guwahati
HJRF 5	Ms. Aishwarya	30.07.2018	Till date	Validation and valuing of >5 selected traditional, ecological knowledge and practices	Dr. USN Murthy, Director, NIPER Guwahati

*If the appointed researcher resigned in the mid of the fellowship duration, then also mention the name of the Himalayan researcher who carried forward the fellowship.

1 INTRODUCTION

1.1 Background/ Summary of the Associateship / Fellowship Study undertaken (max. 500 words)

The North-East region of India contains more than one-third of the country's total biodiversity. The area represents an integral part of Indo Myanmar's biodiversity hotspot, one of 25 global biodiversity hotspots recognized. The eastern Himalayan region support one of the world's richest alpine floras with a high level of endemism (WWF and ICIMOD 2001); (www,biodiversityhotspots.org), Northeast India has India's richest reservoir of plant diversity and supports around 50% of India's total plant diversity (Mao & Hynniewta, 2000). The medicinal plants constitute an essential bio-resource of Northeast India, many of which are used by various ethnic groups for their primary healthcare needs. Most of the populations, especially in the rural areas & different ethnic communities, depending on the oral knowledge of the Traditional Health Practices (THPs), remedies, and therapies to meet their primary health needs. Lack of a detailed database of medicinal plants, their availability, and claimed pharmacological benefits is a challenge hindering the prospects of these traditional systems of medicine in the Himalayan belt. In this regard, a database containing a list of medicinal plants available in the Himalayan belt of the northeast region will be highly beneficial for the modern phyto/pharmaceutical industry.

Additionally, to protect & conserve the endangered plants that are medicinally valued, identifying their plants and their schematic herbarium preparation for an adequate authentication will be of great value to preserve the rich flora of the Himalayan biodiversity. The next step involves exploring the new traditional knowledge systems; an initial screen can help isolate the medically significant properties of plants. The Pharmacological properties and simultaneous analytical characterization of bioactive molecules from the unexplored traditional knowledge systems, and their scientific validation of efficacy, safety and dosage could be of potential value for modern health research. Further, taking the medicinal plants' research outcomes to the Himalayan inhabitants for their rational use creates awareness and sensitization of their importance. This will aid in the, cultivation, conservation, and commercial utility of medicinal plants among the traditional healers & local people of the northeast region. Considering the points mentioned earlier, we have framed the following aim & objectives of the project.

1.2 Baseline and Scope of the Associateship / Fellowship (max. 1000 words)

1.3 Overview of the Major Issues to be addressed (max. 1000 words)

- What makes the North-east India special as bio-diversity reserves? What should be the DBMS format for NE region plants? Which essential plants grow in Himalaya regions which selects

further for initial screening of putative bioactive principles implication in neurological disorders?

- Understanding the traditional and ecological medicinal practices of the Himalayan belt regions. Selection of the traditionally claimed formulations and identify biological action mechanisms in a systemic and scientific manner. To identify which extract/formulation shows maximum efficacy against oxidative stress and, malaria complications?

- Which part of *Zanthoxylum armatum, Elsholtzia communis and Garcinia pedunculata* crude extracts is biologically active? Which solvent fraction shows maximum efficacy in various in-vitro screening models? Which extract shows maximum efficacy against oxidative stress and cancer complications?

- Which part of *Dillenia indica (DI) & Dillenia pentagyna (DP)* crude extracts is biologically active? Which solvent fraction shows maximum efficacy in various in-vitro screening models? Which extract shows maximum efficacy against cancer and cancer complications?

- What are the current scenarios of treatment strategies? What are the reasons behind failure of current therapy? Why there is need of active plant constituents loaded formulations? What is the role of two active plant constituent's selected to make rational combination? Will Janus nanosized emulsion of these active plant constituents solve the problem? What studies to be required to do make it successful?

- What are plants were selected from endangered category? Why there is a need for conserving these plants? What are the harvesting guidelines for endangered plants? What are the guidelines to be followed for conservation of these endangered plants?

- What are the chemical components present in the bioactive extracts? Which components are responsible for the particular activity? How to isolate and characterize the bioactive components from the crude extract?

1.4 Brief summary of the activities under taken by the researcher (max. 1000 words)

[Providing full details of Field study, experimental set up, methods adopted, data collected supported by necessary table, charts, diagrams & photographs (**Data, table and figures should be attached as separate source file (.docx, .xls, jpg, .jpeg, .png, .shp, etc.)].**

Position	**Specific objective**	**Summary of the work done/Deliverables**
HRA001 **(Dr Sahabuddin Ahmed)**	Database development on Himalayan Indigenous Knowledge Systems (IKS) prevailing in NE Hills	Collected the information of around 300 medicinal plants grown in Himalayan region and developed the consolidated database. Development of Digital Library on the above consolidated data is under progress. **Due to paucity of time and COVID pandemic unable to prepare the digital library and will prepare in due course of time as future course of action of the current project.** Also explored the pharmacological evaluation of bioactive components (**Andrographolide, 7,8-Dihydroxyflavone, Hesperidin**) of the medicinal plants grown in Himalayan region for its neuroprotective activity *in vitro* and *in vivo* models. Published three papers in international peer reviewed journals. (Detail report enclosed as **Annexure 1**)
HRA002 **(Dr Deepak Bharadwaj)**	Validation and valuing of >5 selected traditional, ecological knowledge and practices	Prepared database on Traditional formulations used by around 70 number of traditional healers of Northeast Region. Based on traditional usage three traditional healers' formulations (TMH-2, TMC-3 and TMH-11) and extracts of *Dillenia Indica and Dillenia pentagyna* were selected for testing

		anti-malarial activity in *in vitro* and *in vivo* models. All the three formulations and extracts showed potent activity against plasmodium falcifarum in in vitro models. However, efficacy is not as expected in the *in vivo* mice model. Further formulation studies are required to translate these formulations and extracts in the form of products. Published two papers in international peer reviewed journals and two book chapters. (Detail report enclosed as **Annexure 2**)
HJRF001 **(Siddi Jain)**	Pharmacological activities, efficacy, safety and dosage evaluation of bioactive compound in potential species.	Collected, authenticated, extracted and evaluated for biological efficacy of the extracts from the following medicinal plants of *Zanthoxylum armatum (ZA), Elsholtzia communis (EC) and Garcinia pedunculata (GP).* Alcoholic and hydroalcoholic extracts of above plants showed good antioxidant and organo protective activity against doxorubicin and cisplatin induced cardio and nephrotoxicity respectively. Further suitable dosage form development is warranted to translate their use as nutraceuticals or herbal medicines. Published one papers in international peer reviewed journals. (Detail report enclosed as **Annexure 3**
HJRF002 **(Shantanu)**	Pharmacological activities, efficacy, safety and dosage evaluation of bioactive compound in potential species.	Explored the pharmacological evaluation of alcoholic extracts of *Dillenia Indica and Dillenia pentagyna* as adjuvant therapy to prevent the drug induced toxicity and found good protection against cancer

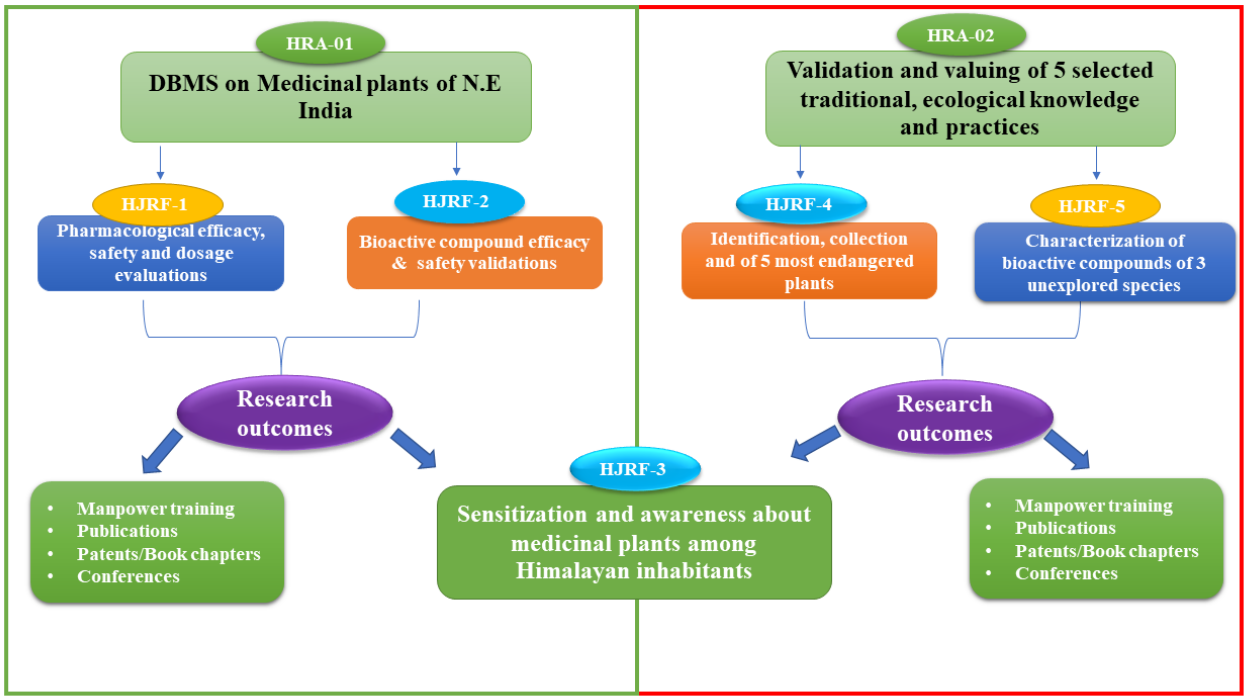
		chemotherapeutic drugs induced organ toxicity. Also evaluated the efficacy of bioactive compounds Hipolon and evodamine against RANKL induced osteoclastogensis and MPTP induced Parkinson's disease. Published three papers in international peer reviewed journals. (Detail report enclosed as **Annexure 4**
HJRF003 **(Dr Datta Pawde)**	**Sensitisation and awareness about medicinal plant among Himalayan in habitants for their rational use**	• Awareness programmes on use and conservation of medicinal plants has been conducted in the villages of Assam, Meghalaya, Arunachal Pradesh, Manipur ad Tripura state • Developed analytical HPLC method for simultaneous estimation of selected two drugs • We have developed a novel nanoformulations for the treatment of rheumatoid arthritis • Visited State Herbal Garden, Kangla Fort, Imphal West, Manipur • Abstract entitled "Systematic Development of Janus Nanosized Emulsions by Quality by Design (QbD) Approach" selected and delivered a short talk in ICANN2019 held at IIT Guwahati campus during December 18-21, 2019 • Visited Kaziranga National Orchid and Biodiversity Park, Kaziranga,

		Assam • Visited Nameri National Park and Forest Reserve, Assam • **Two book chapter has been published** • Presented poster at Virtual DDG India meeting 2020 • Participated in 'International webinar on Quality by Design (QbD)-Industrial Approach' • Participated in 'Entrepreneurship Development Seminar series for Pharma Sector, Part-I' (Detail report enclosed as **Annexure 5)**
HJRF004 **(Dr Vishal Chaudhari)**	**Identification and collection and quantification of 5 most endangered plants with medicinal potential in region**	NIPER-G conducted field survey in different Himalayan rural areas from Assam, Meghalaya, Manipur, Tripura, Arunachal Pradesh and collected *Nepenthes khasiana, Coptis teeta, Shorea assamica, Aquilaria malaccensis, Vanilla planifolia* IUCN Red listed Medicinal plants. **Further efforts will be made in collaboration with state forest department as well as locals for the effective conservation of the above species.** Also developed nanoformulation for quercetin and piperine for the effective delivery to cancer cells. (Detail report enclosed as **Annexure 6)**

HJRF005 **(Aishwarya)**	**Extraction, isolation, purification, characterisation of bioactive compounds from 3 unexplored species**	Extraction and phytochemical characterisation of *Dillinea India, Dillenia Pentagyna and Mesua assamica* were performed by using LCMS HRMS. Published three papers in international peer reviewed journals. (Detail report enclosed as **Annexure 7)**

2 METHODOLOGIES, STARTEGY AND APPROACH

2.1 Methodologies used for the study (max. 1000 words)



2.2 Details of Scientific data collected and Equipments Used (max 500 words)

North-east part of India is rich in plant biodiversity whose healing power has been realized and documented for ages. Plants from North East region of India are being widely used by local people for treatment for various diseases as well as a part of their regular diet. The scientific evidence on the biological as well as chemical properties of these plants is very limited and therefore it is important to characterize the medicinal importance of each plant. Thus, the aim of the study is extraction, isolation, purification and characterization of bioactive compounds from 3 unexplored species from North-east region of India. In this regard we have collected *Dillenia pentagyna* (NIPER/18/01), *Clerodendrum hexangularis* (NIPER/18/08), and *Dillinea indica* (NIPER/18/11) from North-east region of India due to their high availability. These plants were selected for further

phytochemical investigations based on the in-house *in vitro* testing by our *HJRF-1* and *HJRF-2* on anti-oxidant and organo-protective activities. To develop chemical fingerprints of bioactive extracts LC-MS approach has been selected for rapid identification and de-replication of components. In order to identify the chemical constituents responsible for the biological activity the plant parts were dried and extracted in different solvents namely, hexane, chloroform, ethyalcetate, ethanol, and hydro-alcohol (1:1) and subjected for characterization by using analytical techniques

2.3 Primary Data Collected (max 500 words)

NIPER-G conducted field survey in different Himalayan rural areas from Assam, Meghalaya, Manipur, Tripura, Arunachal Pradesh. We collected Nepenthes khasiana, Coptis teeta, Shorea assamica, Aquilaria malaccensis, Vanilla planifolia IUCN Red listed Medicinal plants. For collection of IUCN Red listed species we have taken proper permission from Assam State Biodiversity Board & Assam Forest Department, Kamrup Division & from CSIR-NEIST, Jorhat & prepared herbarium for proper authentication of identified species. We have also received the Accession No. of authentication from Assam Bioresources Centre, Madan Kamdev, Baihata Chariali, ASTEC, and Assam. Along with this we have also collected Mesua assamica which was previously in the IUCN Red listed Endangered category. Through proper propagation, it has been up lifted to threatened category.

2.4 Details of Field Survey arranged (max 500 words)

NIPER-G conducted field survey in different Himalayan rural areas from Assam, Meghalaya, Manipur, Tripura, Arunachal Pradesh.

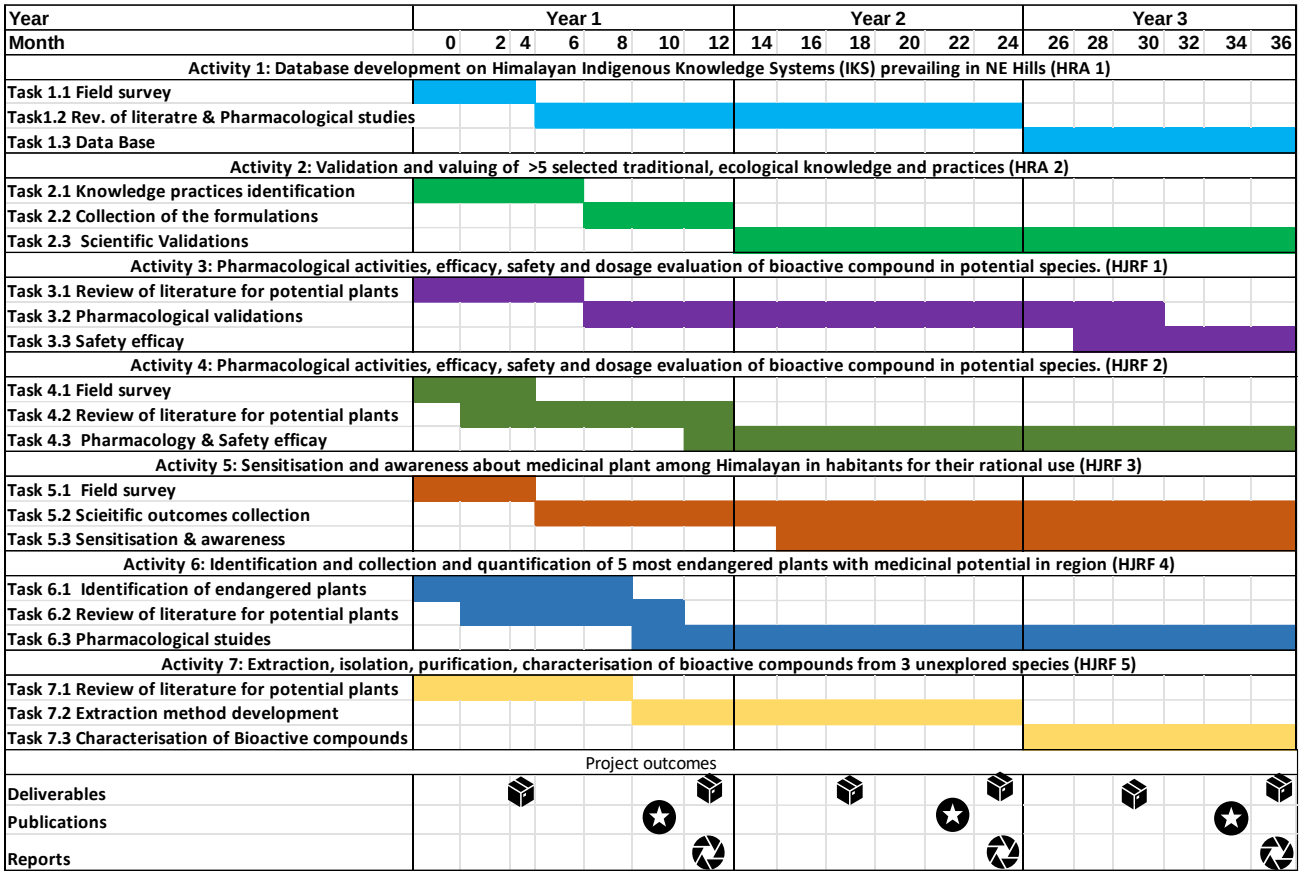
2.5 Strategic Planning for each Activities (max. 1000 words)

Activity 1: Database development on Himalayan Indigenous Knowledge Systems (IKS) prevailing in NE Hills	Initially, a team of the HRA/HJRFs have visited various rural Himalayan regions and collected information on the medicinally and economically valued plants available in the area. A separate list focus on the plants listed under the endangered category was made and documented. A thorough review of the potentially valued plants from the Himalayan belt and a database preparation was planned. We intended to incorporate various keywords like, Botanical name, local name/s, chemical constituents, reported properties, taxonomy, useful parts of the plants for easy search of the plants in the database. **Due to paucity of time and COVID pandemic unable to prepare the digital library and will prepare in due course of time as future course of action of the current project**

Activity 2: Validation and valuing of >5 selected traditional, ecological knowledge and practices	The NIPER Guwahati, considering the rich and diverse knowledge practices available in the rural areas, has conducted a traditional healers meeting. The idea of the meeting is to collect the data from them and facilitate their scientific validations for the claimed therapeutic applications. Further agreements (Mou's) were planned to establish them as potential entrepreneurs in the northeast regions. In this way, their practices will be sustained and accepted by modern medicine, thereby improving their economic status.
Activity 3: Pharmacological activities, efficacy, safety and dosage evaluation of bioactive compound in potential species.	We have further planned to test and validate the new medicinal plants for their pharmacological, safety, and dosage parameters in best possible methods or models.
Activity 4: Pharmacological activities, efficacy, safety and dosage evaluation of bioactive compound in potential species.	We have further planned to test and validate the unexplored medicinal plants for their pharmacological, safety, and dosage parameters in the best possible methods or models. The outcomes of activities 3,4 were planned for communication in the peer-reviewed journals so that the pharmaceutical or medical communities can accept them. **The data generated from the current project on exploration of medicinal plants of NE India used by traditional healers or locals for the treatment of various diseases are tested for its efficacy and safety will be further translate to develop nutraceutical products as per the FSSAI regulatory requirements as future scope of the current project**
Activity 5: Sensitisation and awareness about medicinal plant among Himalayan in habitants for their rational use	We intend to create an awareness of the potential therapeutic applications of the medicinal plants or knowledge practices to the wide range of rural habitants for their rational usage. We have planned to conduct the sensitization and awareness programs at various proposed regions.
Activity 6: Identification and	Further from the data obtained by the database, we plan to collect

collection and quantification of 5 most endangered plants with medicinal potential in region	the 5 most endangered plants with potential medicinal applications. This idea is to uplift their propagation by creating the sensitization to the habitants. Also, the pharmacological values were planned to test and validate scientifically and **Further efforts also will be made in collaboration with state forest department as well as locals for the effective conservation of the above species.**
Activity 7: Extraction, isolation, purification, characterisation of bioactive compounds from 3 unexplored species	Finally, we intended to extract and purify the bioactive molecules from the new species and establish them as potential phytopharmaceutical materials in the market.

2.6 Activity-wise Timeframe followed using Gantt/ PERT Chart (max. 1000 words)



3 KEY FINDINGS AND RESULTS

3.1 Major Research Findings (max. 1000 words)

NIPER-Guwahati, under the NMHS project, selected almost 300 medicinal plants from different adjoining Himalayan N.E Region & prepared a Database. The database includes parameters like Taxonomy of the plant, Vernacular name, habitat & distribution, the ideal time of collection plant parts used, reported chemical constituents, reported traditional medicinal uses, their mode of administration, extraction techniques & said Patent & marketing products. The Database preparation is mainly concentrated on conserving this Traditional Medicinal Knowledge with a DBMS system. It is often seen that traditional knowledge has tremendous application in drug discovery. The development of modern science and technologies, notably biotechnology and information technologies, have increased the value of biodiversity and associated knowledge, including traditional knowledge. Moreover, with growing evidence of active phytoconstituents within indigenous species of northern Himalayan regions, plants such as *Andrographis paniculata, Carallia brachiata, Senna siamea* (as seen in DBMS system) have been found to contains important bio-active compounds composed of Andrographolide (*Andrographis paniculata*), Hesperidin, 7,8-Dihydroxyflavone (*Carallia brachiata, Senna siamea*) which possess potent anti-inflammatory, antioxidant, anti-apoptotic activities in various diseases and neurological disease.

Hence, we further evaluated these new active principles (Andrographolide, 7,8-Dihydroxyflavone, Hesperidin) in *in-vitro, in-vivo* models of Parkinson's disease, Huntington's disease and *in-vivo* model of hesperidin against depressive-anxiety like behavior (elucidated in chronic stress and LPS mice model). Hence, we can conclude that the diverse floras within the Himalayas region are being flourished with diverse bio-actives principles that can be used in several detrimental neurological disorders and other bodily diseases.

On behalf of NIPER, we intend to explore the new traditional and ecological knowledge-based practices in the Himalayan belt regions of North-east states. We have initially conducted outreach, and traditional healers meet programs in India's northeast states to meet this objective. The first traditional healers meet organized at the NIPER (Guwahati, August 2018), followed by Dhemaji Dist (Assam), Joai Dist (Meghalaya), Majuli Dist (Assam, Dec 2019), Dhemaji (Assam, Nov 2020), Jorhat (Assam, Nov 2020), Nansai Dist (Arunachal Pradesh Nov 2020) and Barpeta Dist (Assam, Nov 2020).

With these programs, we have met several healers who were enthusiastic in providing their formulations to validate them scientifically for various biological claims with the state-of-art research facilities at the NIPER Guwahati. Among them, nine traditional healers have provided us with their traditional formulations to validate them against Diabetes, Malaria, and hepatoprotective properties. A confidentiality non-disclosure agreement was made between the traditional healers, and the NIPER G was created to protect the traditional knowledge. Under the current objective, we tested the *in-vitro* anti-malarial efficacy of the traditional healer formulations (3 number) as well alcoholic extracts of *Dillinea Indica*, *Dillinea pentagyna* showed good anti-malarial activity in *in vitro* model compared to the respective control groups. However, the efficacy was not pronounced in the in-vivo studies. We presume that the poor bioavailability of the traditional formulations as well extracts could be a reason for low anti-malarial activity therefore an appropriate delivery system need to be developed for the better therapeutic efficacy.

Approximately 50% of the new drugs introduced in the market are of natural resource. These natural resources are majorly from North-East Himalayan region. *Zanthoxylum armatum (ZA), Elsholtzia communis (EC) and Garcinia pedunculata (GP)* were used by local people of Himalayan region as food material and also for therapeutic application as traditional use. However, there is no scientific validation about their importance as medicinal plants as well as food material. Oxidative stress (OS) is one of the principal factors mainly responsible for various ailments. Drug/disease/pollution/stress induces organ toxicity via generating enormous OS in body leading to deleterious effects. On the other hand, most of the herbal and pharmaceutical industries are searching for a good natural antioxidants of natural origin. As above selected natural plants are taken by local people of the Himalayan region and are indicated to be safe for human use.

Therefore, we want to explore the potential use of these medicinal plants as an antioxidant molecule. In order to achieve this we have collected, authenticated, extracted these medicinal plants and found that alcoholic and hydroalcoholic extracts of ZA, EC and GP have good free radical scavenging activity when compared with reference standard like ascorbic acid.

Further we also tested the effect of hydroalcoholic extracts in in-vitro and in-vivo models for their organo protective activity. We found that these extracts have shown potential protection against doxorubicin and cisplatin induced cardio and nephrotoxicity respectively in in-vitro and in-vivo model. This study highly concludes that there is a potential clinical translational of these medicinal plants as adjuvant therapy along with chemotherapy drugs like doxorubicin and cisplatin which may reduce side effects at the time of chemotherapy to cancer patients and also enhance cancer efficacy. Hence pre-clinical toxicity studies are required for their potential use as antioxidants as well as adjuvant therapy along with chemotherapy.

Local healer presently we discovered *Dillenia indica (DI) and Dillenia pentagyna* (DP) endogenous to Himalayan region of North-East India, has been used locally to treat various clinical pathologies like Antileukemia, antidiabetic, antimicrobial, cytotoxicity, traditional uses, nociceptive activity. But its efficacy against cancer and chemotherapy induced complications is still yet to be explored. Thus, aim of our study is to explore efficacy of these natural extracts in various cancerous cell lines and in-vivo model of chemotherapy induced complications. In order to explore for antioxidant properties of DI and DP, we performed a battery of antioxidant assays of various solvent extracts of DI and DP. We found hydroalcoholic fraction of DI and DP superior to standard ascorbic acid. Thus, we screened hydroalcoholic extracts of DI and DP against doxorubicin induced cardiotoxicity and cisplatin induced nephrotoxicity both in vitro and in vivo. We found the results hydroalcoholic extracts of DI and DP were very effective in attenuating the cytotoxicity caused by anticancer drugs like doxorubicin and cisplatin in cardiac (H9C2) and kidney (HEK293) cell line. In vivo study showed the treatment with hydroalcoholic extracts also reversed the biochemical, histological and functional changes induced by doxorubicin and cisplatin in cardiac and kidney parameters. Further investigation into molecular mechanism behind nephroprotective activity of DI and DP is under progress. The extracts were also evaluated for its anticancer effects where, we found that chloroform and ethyl acetate fraction possessed significant anticancer activity in oral and colon cancer cell. Further exploring for the pharmacological activities for Himalayan plants, we also screened Hispolon a bioactive compound from obtained from Phellinus linteus (endemic to Sikkim and Himachal Pradesh) for its activity against RANKL induced osteoclastogenesis in vitro. We found Hisplon inhibited osteoclastogenesis by downregulating NFATc1 and c-FOS expression. Thirdly, we explored for the neuroprotective effects of Evodamine a phytoconstituent isolated from *Evodia rutaecarpa, and Evodia fraxinifolia* H.K found in Sikkim both in *in vitro* and *in vivo* model.

Overall, these studies will impart a scientific validation to these identified Himalayan plants, which will enhance conservation, commercial value and research and development in North-East region.

We have conducted an outreach program in the different Himalayan region of Northeast India to create awareness about the uses, cultivation and conservation of medicinal plants among the traditional healers & local people. Till date, we have organized an awareness program in villages of Assam, Arunachal Pradesh, Manipur and Meghalaya. More than 500 people participated in the awareness programs that included the traditional healers, farmers, college students from different ethnic communities, and researchers from different research institutes. Farmers were pleased by knowing the medicinal value of the plants cultivated in their field. Traditional healers, college students, and researchers from different research institutes are motivated to conserve medicinal plants in the Himalayan region of Northeast India. We have also developed novel nanosized emulsion for the treatment of rheumatoid arthritis and organized several outreach programs. As an outcome of the project, we have published two book chapters and a research article in the verge of communication. We also planned to conduct the awareness program in Assam, Arunachal Pradesh, Sikkim and Tripura. Database on high-value Medicinal plants and their traditional use was also developed.

On behalf of NIPER-G, conducted field survey in different Himalayan rural areas of Assam, Meghalaya, Manipur, Tripura, and Arunachal Pradesh. We have collected Nepenthes *khasiana, Coptis teeta, Shorea assamica, Aquilaria malaccensis, Vanilla planifolia* IUCN Red listed Medicinal plants. For collection of IUCN Red listed species we have taken proper permission from Assam State Biodiversity Board & Assam Forest Department, Kamrup Division and from CSIR-NEIST, Jorhat. A schematic herbarium is prepared for adequate authentication for identified species. We have also received the Accession No. of authentication from Assam Bioresources Center, Madan Kamdev, Baihata Chariali, ASTEC, and Assam. We have also collected *Mesua assamica*, which was previously in the IUCN Red listed Endangered category. Through proper propagation, it has been up-lifted to the threatened category. Due to constraints in collecting these endangered plants, we tested the anticancer activities for *M. assamica in in-vitro* models, including cell viability assay. The whole study was performed in cancer cell lines like breast and colon cancer, and found that alcoholic extract and ethyl acetate extract showed potential biological activity. Further studies are in progress with the final optimized extracts.

We have also developed nanoformulation containing bio-flavonoids as active constituents that are present in these plants. Therefore nanoformulation was developed and characterized for its physicochemical properties and its in-vitro cellular evaluation against oral cancer cell line. This provides a translational form to deliver active constituents enriched nano-carriers to mitigate oral cancer burden in the N.E. region.

Plant 1-*Dillenia pentagyna (DP*): Firstly, all the extracts of DP were evaluated for the in-vitro anti-oxidant, cardioprotective and hepatoprotective activity and in-vivo cardioprotective, nephroprotective and hepatoprotective activity by JRF-02. The hydro-alcoholic extract of DP showed significant antioxidant and organo-protective activity. The ethanolic extract of DP showed good anti-cancer activity. Hence, LC-MS/MS analysis was performed to determine the chemical constituents. The LC-MS/MS analysis of an ethanolic extract of DP detected 13 major compounds in both positive and 4 compounds in negative ESI ionization mode. The hydro-alcoholic extract of DP was found to be active in H9C2 cell line. It showed protective activity against doxorubicin-induced cardiotoxicity and cisplatin-induced nephrotoxicity and further fractionated by using the flash chromatographic technique, 4 fractions in normal phase and 3 fractions from reverse-phase were collected and subjected to biological activity testing. The fractions collected in the reverse phase showed biological activity. The 3 bioactive fractions namely DP-F1, DP-F2, and DP-F3 were subjected to HPLC analysis to detect the biological activity's biomarker components. Many components were detected in each fraction which may be responsible for the biological activity. The bioactive F1 revealed 4 compounds in the positive [M+H]+ mode and 26compounds in the negative [M-H]-mode. Further characterization of the components and purification is under progress.

Plant 2-Dillenia Indica (DI): Similarly, all the extracts of DI were evaluated by JRF-02 for the in-vitro anti-oxidant, cardioprotective and hepatoprotective activity and in-vivo cardioprotective, nephroprotective and hepatoprotective activity. Simultaneously the chemical constituents of DI were characterized by LC-MS/MS. Among all extracts hydro-alcoholic extract showed significant anti-oxidant and organo-protective activity. We have identified chemical constituents from bioactive extracts of DI, 37 compounds in chloroform, 77 compounds in ethyl acetate, and 90 compounds in ethanol, 73 compounds in hydro-alcoholic extract. Further fractionation, purification and identification of the components is under progress. To develop chemical fingerprints of bioactive extracts an LC-MS/MS method was optimized for polyphenols and amino acids to quantify chemical in the bioactive extracts.

3.2 Key Results (max. 1000 words in bullets covering all activities)

- Collected the information of around 300 medicinal plants grown in Himalayan region and developed the consolidated database. Development of Digital Library on the above consolidated data is under progress. Also explored the pharmacological evaluation of bioactive components (Andrographolide, 7,8-Dihydroxyflavone, Hesperidin) of the medicinal plants grown in Himalayan region ameliorated neuroprotective activity in vitro and in vivo models.

- Prepared database on traditional formulations used by around 70 number of traditional healers of Northeast Region. Based on traditional usage three traditional healers' formulations (*TMH-2, TMC-3 and TMH-11*) and extracts of *Dillenia Indica and Dillenia pentagyna* were

selected for testing anti-malarial activity in in vitro and in vivo models. All the three formulations and extracts showed potent activity against plasmodium falcifarum in *in vitro* models. However, efficacy is not as expected in the in vivo mice model. Further formulation studies are required to translate these formulations and extracts in the form of products.

- Collected, authenticated, extracted and evaluated for biological efficacy of the extracts from the following medicinal plants of *Zanthoxylum armatum (ZA), Elsholtzia communis (EC) and Garcinia pedunculata (GP).* Alcoholic and hydroalcoholic extracts of above plants showed good antioxidant and organo protective activity against doxorubicin and cisplatin induced cardio and nephrotoxicity respectively. Further suitable dosage form development is warranted to translate their use as nutraceuticals or herbal medicines.

- Explored the pharmacological evaluation of alcoholic extracts of *Dillenia Indica and Dillenia pentagyna* as adjuvant therapy to prevent the drug induced toxicity and found good protection against cancer chemotherapeutic drugs induced organ toxicity. Also evaluated the efficacy of bioactive compounds Hipolon and evodamine against RANKL induced osteoclastogensis and MPTP induced Parkinson's disease.

- Awareness programmes on use and conservation of medicinal plants has been conducted in the villages of Assam, Meghalaya, Arunachal Pradesh, Manipur ad Tripura state

- We have developed a novel nanoformulations for the treatment of rheumatoid arthritis

- NIPER-G conducted field survey in different Himalayan rural areas from Assam, Meghalaya, Manipur, Tripura, Arunachal Pradesh and collected Nepenthes khasiana, *Coptis teeta, Shorea assamica, Aquilaria malaccensis, Vanilla planifolia* IUCN Red listed Medicinal plants. Also developed nanoformulation for quercetin and piperine for the effective delivery to cancer cells

- Extraction and phytochemical characterisation of *Dillinea India, Dillenia Pentagyna* and *Mesua assamica* were performed by using LCMS HRMS.

3.3 Conclusion of the study undertaken (maximum 500 words in bullets)

The development of modern science and technologies, notably biotechnology and information technologies, have increased the value of biodiversity and associated knowledge, including traditional knowledge. Moreover, with growing evidence of active phytoconstituents within indigenous species of northern Himalayan regions, We have worked for the listing, scientific validation, and analytical characterisation of the potential traditional systems of medicine. Initially, we have selected almost 300 medicinal plants from different adjoining

Himalayan N.E Region & prepared an online data Database. Further, three traditional healers formulations were scientifically validated and provided a scientific validation for claimed biological properties. A confidentiality non-disclosure agreement was made between the traditional healers, and the NIPER G to protect the traditional knowledge. Some of the unexplored medicinal plants were also characterised for the bioactive molecules responsible for the pharmacological properties which paved a way for their scale-up method development and further translations. The research outcomes were carried to the inhabitants of the northeast Himalayan belt inhabitants (villages of Assam, Arunachal Pradesh, Manipur and Meghalaya) to sensitise and create an awareness. More than 500 people participated in the awareness programs that included the traditional healers, farmers, college students from different ethnic communities, and researchers from different research institutes. Farmers were pleased by knowing the medicinal value of the plants cultivated in their field. Overall, the proposed project was able to uplift the scientific evidence of the traditional knowledge practices, create an awareness to the inhabitants about the commercial & biological value simultaneously publishing the research outcomes in peer reviewed publications.

4 OVERALL ACHIEVEMENTS

4.1 Achievements on Objectives [Defining contribution of deliverables in overall Mission (max. 1000 words)]

- Collected the information of around 300 medicinal plants grown in Himalayan region and developed the consolidated database. Development of Digital Library on the above consolidated data is under progress. Also explored the pharmacological evaluation of bioactive components (Andrographolide, 7,8-Dihydroxyflavone, Hesperidin) of the medicinal plants grown in Himalayan region for its neuroprotective activity in vitro and in vivo models. Published three papers in international peer reviewed journals.

- Prepared database on Traditional formulations used by around 70 number of traditional healers of Northeast Region. Based on traditional usage three traditional healers' formulations (TMH-2, TMC-3 and TMH-11) and extracts of Dillenia Indica and Dillenia pentagyna were selected for testing anti-malarial activity in in vitro and in vivo models. All the three formulations and extracts showed potent activity against plasmodium falcifarum in in vitro models. However, efficacy is not as expected in the in vivo mice model. Further formulation studies are required to translate these formulations and extracts in the form of products. Published two papers in international peer reviewed journals and two book chapters.

- Collected, authenticated, extracted and evaluated for biological efficacy of the extracts from the following medicinal plants of Zanthoxylum armatum (ZA), Elsholtzia communis (EC) and Garcinia pedunculata (GP). Alcoholic and hydroalcoholic extracts of above plants showed good antioxidant

and organo protective activity against doxorubicin and cisplatin induced cardio and nephrotoxicity respectively. Further suitable dosage form development is warranted to translate their use as nutraceuticals or herbal medicines.Published one papers in international peer reviewed journals.

- Explored the pharmacological evaluation of alcoholic extracts of Dillenia Indica and Dillenia pentagyna as adjuvant therapy to prevent the drug induced toxicity and found good protection against cancer chemotherapeutic drugs induced organ toxicity. Also evaluated the efficacy of bioactive compounds Hispolon and evodamine against RANKL induced osteoclastogensis and MPTP induced Parkinson's disease.
    - Published three papers in international peer reviewed journals. Awareness programmes on use and conservation of medicinal plants has been conducted in the villages of Assam, Meghalaya, Arunachal Pradesh, Manipur ad Tripura state
    - Developed analytical HPLC method for simultaneous estimation of selected two drugs
    - We have developed a novel nanoformulations for the treatment of rheumatoid arthritis
    - Visited State Herbal Garden, Kangla Fort, Imphal West, Manipur
    - Abstract entitled "Systematic Development of Janus Nanosized Emulsions by Quality by Design (QbD) Approach" selected and delivered a short talk in ICANN2019 held at IIT Guwahati campus during December 18-21, 2019
    - Visited Kaziranga National Orchid and Biodiversity Park, Kaziranga, Assam
    - Visited Nameri National Park and Forest Reserve, Assam
    - Two book chapter has been published
    - Presented poster at Virtual DDG India meeting 2020
    - Participated in 'International webinar on Quality by Design (QbD)-Industrial Approach'
    - Participated in 'Entrepreneurship Development Seminar series for Pharma Sector, Part-I'
- NIPER-G conducted field survey in different Himalayan rural areas from Assam, Meghalaya, Manipur, Tripura, Arunachal Pradesh and collected Nepenthes khasiana, Coptis teeta, Shorea assamica, Aquilaria malaccensis, Vanilla planifolia IUCN Red listed Medicinal plants. Also developed nanoformulation for quercetin and piperine for the effective delivery to cancer cells. 6)
- Extraction and phytochemical characterisation of Dillinea India, Dillenia Pentagyna and Mesua assamica were performed by using LCMS HRMS.Published three papers in international peer

reviewed journals. Establishing New Database/Appending new data over the Baseline Data (max. 1500 words, in bullet points)

4.2 Generating Model Predictions for different variables (if any) (max 1000 words in bullets)
4.3 Technological Intervention (max. 1000 words): NA
4.4 On-field Demonstration and Value-addition of Products (max. 1000 words, in bullet points): NA
4.5 Developing Green Skills in IHR: NA
4.6 Addressing Cross-cutting Issues (max. 500 words, in bullet points): NA

5 IMPACTS OF FELLOWSHIP IN IHR

5.1 **Socio-Economic Development (max. 500 words, in bullet points):** Scientific validation of the traditional knowledge and local use of medicinal plants of NE Himalayas at NIPERG under this project gave addition to the selected tested medicinal plants. We assume that this value addition to these medicinal plants may improve the socioeconomic status of the local farmers living in these Himalayan regions and it required some more studies to take up these data by the industries to translate the use of the selected medicinal plants for therapeutic applications.

5.2 Scientific Management of Natural Resources In IHR (max. 500 words, in bullet points)
Database for medicinal plants prepared under the current project may help the future scientist/himlayan scholars to develop strategies for the effective managemnent of natural resources.

5.3 Protection of Environment (max. 500 words, in bullet points)
NA

5.4 Developing Mountain Infrastructures (max. 500 words, in bullet points)
NA

5.5 Strengthening Networking in IHR (max. 700 words, in bullet points)
NA

6 EXIT STRATEGY AND SUSTAINABILITY

6.1 How effectively the fellowship findings could be utilized for the sustainable development of IHR (max. 1000 words)
Herein, we opted phasing down Exit Strategy

Phasing down: Under this strategy, we opted for a gradual reduction of this program activities, utilizing full involvement of all recruited manpower under this project to sustain project outcomes & also to achieve the proposed research objectives.

6.2 Efficient ways to replicate the outcomes of the fellowship in other parts of IHR (max. 1000 words)
As mentioned above, there is a lot of scopes for exploring the use of these medicinal plants in the treatment of various diseases. They may replicate similar extraction procedures and develop the extracts which may be further used for biological activities as well as a phytochemical characterization to develop phytopharmaceuticals/ nutraceuticals/herbal products.

6.3 Identify other important areas not covered under this study, but needs further attention (max. 1000 words):

Alcoholic and hydroalcoholic extracts *of Dillenia Indica and Dillenia pentagyna* showed good anti oxidant and anti inflammatory properties may further explore their use for the treatment of various inflammatory diseases like rheumatoid arthritis, ulcerative colitis, COPD etc., similarly the bioactive compounds 7,8 dihydroxy flavone, andrographolide which showed good neuroprotective activity may be further tested for their toxicity and develop suitable dosage forms for their use for the treatment of neurodegenerative diseases. Development of suitable dosage forms for the traditional healer's formulations which showed good anti malarial activity in the in vitro models to improve bioavailability of the constituents and to improve the therapeutic efficacy may be considered as future studies.

6.4 Major recommendations for sustaining the outcomes of the fellowship in future (500 words in bullets)

Same as mentioned in section 6.3

7 REFERENCES/BIBLIOGRAPHY

1) Ahmed, S., Mundhe, N., Borgohain, M., Chowdhury, L., Kwatra, M., Bolshette, N., Ahmed, A., Lahkar, M., 2016. Diosmin Modulates the NF-kB Signal Transduction Pathways and Downregulation of Various Oxidative Stress Markers in Alloxan-Induced Diabetic Nephropathy. Inflammation 39, 1783-1797.

2) Banagozar Mohammadi, A., Torbati, M., Farajdokht, F., Sadigh-Eteghad, S., Fazljou, S.M.B., Vatandoust, S.M., Golzari, S.E.J., Mahmoudi, J., 2019. Sericin alleviates restraint stress induced depressive- and anxiety-like behaviors via modulation of oxidative stress, neuroinflammation and apoptosis in the prefrontal cortex and hippocampus. Brain Res 1715, 47-56.

3) Bronner, D.N., Abuaita, B.H., Chen, X., Fitzgerald, K.A., Nunez, G., He, Y., Yin, X.M., O'Riordan, M.X., 2015. Endoplasmic Reticulum Stress Activates the Inflammasome via NLRP3- and Caspase-2-Driven Mitochondrial Damage. Immunity 43, 451-462.

4) Chakrabarti, S., 2018. Mood disorders in the international classification of Diseases-11: Similarities and differences with the diagnostic and statistical manual of mental Disorders 5 and the international classification of Diseases-10. Indian Journal of Social Psychiatry 34, 17-22.

5) Chen, H., Tang, X., Zhou, B., Zhou, Z., Xu, N., Wang, Y., 2017. A ROS-mediated mitochondrial pathway and Nrf2 pathway activation are involved in BDE-47 induced apoptosis in Neuro-2a cells. Chemosphere 184, 679-686.

6) Choubey, P., Kwatra, M., Pandey, S.N., Kumar, D., Dwivedi, D.K., Rajput, P., Mishra, A., Lahkar, M., Jangra, A., 2019. Ameliorative effect of fisetin against lipopolysaccharide and restraint stress-induced behavioral deficits via modulation of NF-κB and IDO-1. Psychopharmacology (Berl) 236, 741-752.

7) Choudhury, S., Ghosh, S., Gupta, P., Mukherjee, S., Chattopadhyay, S., 2015. Inflammation-induced ROS generation causes pancreatic cell death through modulation of Nrf2/NF-kappaB and SAPK/JNK pathway. Free Radic Res 49, 1371-1383.

8) Cobley, J.N., Fiorello, M.L., Bailey, D.M., 2018. 13 reasons why the brain is susceptible to oxidative stress. Redox Biol 15, 490-503.

9) Couch, Y., Trofimov, A., Markova, N., Nikolenko, V., Steinbusch, H.W., Chekhonin, V., Schroeter, C., Lesch, K.P., Anthony, D.C., Strekalova, T., 2016. Low-dose lipopolysaccharide (LPS) inhibits aggressive and augments depressive behaviours in a chronic mild stress model in mice. J Neuroinflammation 13, 108.

10) Dang, R., Guo, Y.-y., Zhang, K., Jiang, P., Zhao, M.-g., 2019. Predictable chronic mild stress promotes recovery from LPS-induced depression. Molecular Brain 12, 42.

11) Dulawa, S.C., Holick, K.A., Gundersen, B., Hen, R., 2004. Effects of chronic fluoxetine in animal models of anxiety and depression. Neuropsychopharmacology 29, 1321-1330.

12) Dwivedi, D.K., Kumar, D., Kwatra, M., Pandey, S.N., Choubey, P., Lahkar, M., Jangra, A., 2018. Voluntary alcohol consumption exacerbated high fat diet-induced cognitive deficits by NF-κB-calpain dependent apoptotic cell death in rat hippocampus: Ameliorative effect of melatonin. Biomed Pharmacother 108, 1393-1403.

13) Abramovič, H., Grobin, B., Ulrih, N.P., and Cigić, B. (2017). The methodology applied in DPPH, ABTS and Folin-Ciocalteau assays has a large influence on the determined antioxidant potential. Acta Chimica Slovenica 64, 491-499.

14) Alizadeh Behbahani, B., and Shahidi, F. (2019). Melissa officinalis essential oil: Chemical compositions, antioxidant potential, total phenolic content and antimicrobial activity. Nutrition and Food Sciences Research 6, 17-25.

15) Battu, S., Afroz, S., Giddaluru, J., Naz, S., Huang, W., Khumukcham, S.S., Khan, R.A., Bhat, S.Y., Qureshi, I.A., and Manavathi, B. (2018). Amino acid starvation sensing dampens IL-1β production by activating riboclustering and autophagy. PLoS biology 16, e2005317.

16) Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R.L., Torre, L.A., and Jemal, A. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians 68, 394-424.

17) Brown, S.-A., Sandhu, N., and Herrmann, J. (2015). Systems biology approaches to adverse drug effects: the example of cardio-oncology. Nature Reviews Clinical Oncology 12, 718.

18) Conklin, K.A. (2004). Cancer chemotherapy and antioxidants. The Journal of nutrition 134, 3201S-3204S.

19) Cuadrado, A., Rojo, A.I., Wells, G., Hayes, J.D., Cousin, S.P., Rumsey, W.L., Attucks, O.C., Franklin, S., Levonen, A.-L., and Kensler, T.W. (2019). Therapeutic targeting of the NRF2 and KEAP1 partnership in chronic diseases. Nature Reviews Drug Discovery 18, 295-317.

20) Howden, R. (2013). Nrf2 and Cardiovascular Defense Oxid. Med. Cell. Longevity 104308.

21) Huang, Q., Zhou, H.J., Zhang, H., Huang, Y., Hinojosa-Kirschenbaum, F., Fan, P., Yao, L., Belardinelli, L., Tellides, G., and Giordano, F.J. (2015). Thioredoxin-2 inhibits mitochondrial reactive oxygen species generation and apoptosis stress kinase-1 activity to maintain cardiac function. Circulation 131, 1082-1097.

22) Hwang, J.-T., Kwon, D.Y., Park, O.J., and Kim, M.S. (2008). Resveratrol protects ROS-induced cell death by activating AMPK in H9c2 cardiac muscle cells. Genes & nutrition 2, 323-326.

23) Koul, A., Goyal, R., and Bharati, S. (2014). Protective effect of Azadirachta indica A. Juss against doxorubicin-induced cardiac toxicity in tumour bearing mice.

24) Müller, L., Fröhlich, K., and Böhm, V. (2011). Comparative antioxidant activities of carotenoids measured by ferric reducing antioxidant power (FRAP), ABTS bleaching assay (αTEAC), DPPH assay and peroxyl radical scavenging assay. Food Chemistry 129, 139-148.

25) Ohkawa, H., Ohishi, N., and Yagi, K. (1979). Assay for lipid peroxides in animal tissues by thiobarbituric acid reaction. Analytical biochemistry 95, 351-358.

26) Owen, J.B., and Butterfield, D.A. (2010). "Measurement of oxidized/reduced glutathione ratio," in Protein misfolding and cellular stress in disease and aging. Springer), 269-277.

27) Peoples, J.N., Saraf, A., Ghazal, N., Pham, T.T., and Kwong, J.Q. (2019). Mitochondrial dysfunction and oxidative stress in heart disease. Experimental & Molecular Medicine 51, 1-13.

28) Prathumsap, N., Shinlapawittayatorn, K., Chattipakorn, S.C., and Chattipakorn, N. (2020). Effects of doxorubicin on the heart: From molecular mechanisms to intervention strategies. European journal of pharmacology 866, 172818.

29) Pugazhendhi, A., Edison, T.N.J.I., Velmurugan, B.K., Jacob, J.A., and Karuppusamy, I. (2018). Toxicity of Doxorubicin (Dox) to different experimental organ systems. Life sciences 200, 26-30.

30) Rugo, H.S., Olopade, O.I., Demichele, A., Yau, C., Van't Veer, L.J., Buxton, M.B., Hogarth, M., Hylton, N.M., Paoloni, M., and Perlmutter, J. (2016). Adaptive randomization of veliparib–carboplatin treatment in breast cancer. New England Journal of Medicine 375, 23-34.

31) Saiful Yazan, L., and Armania, N. (2014). Dillenia species: A review of the traditional uses, active constituents and pharmacological properties from pre-clinical studies. Pharmaceutical biology 52, 890-897.

32) Sharma, H.K., Chhangte, L., and Dolui, A.K. (2001). Traditional medicinal plants in Mizoram, India. Fitoterapia 72, 146-161.

33) Sheibani, M., Nezamoleslami, S., Faghir-Ghanesefat, H., Hossein Emami, A., and Dehpour, A.R. (2020). Cardioprotective effects of dapsone against doxorubicin-induced cardiotoxicity in rats. Cancer Chemotherapy and Pharmacology, 1-9.

34) Wang, P., Geng, J., Gao, J., Zhao, H., Li, J., Shi, Y., Yang, B., Xiao, C., Linghu, Y., and Sun, X. (2019). Macrophage achieves self-protection against oxidative stress-induced ageing through the Mst-Nrf2 axis. Nature communications 10, 1-16.

35) Xu, S., Wang, Y., Yu, M., Wang, D., Liang, Y., Chen, Y., Liao, C., Xie, Z., Zhao, B., and Han, J. (2020). LongShengZhi capsule inhibits doxorubicin-induced heart failure by anti-oxidative stress. Biomedicine & Pharmacotherapy 123, 109803.

36) Yadav, R.K., and Srivastava, S.K. (2014). Monitoring in vitro phytochemical analysis of some diabetic plants and its utilization. Annals of Phytomedicine 3, 35-39.

37) Zhang, X., Hu, C., Kong, C.-Y., Song, P., Wu, H.-M., Xu, S.-C., Yuan, Y.-P., Deng, W., Ma, Z.-G., and Tang, Q.-Z. (2020). FNDC5 alleviates oxidative stress and cardiomyocyte apoptosis in doxorubicin-induced cardiotoxicity via activating AKT. Cell Death & Differentiation 27, 540-555.

38) Shankar R, Rawat MS. Conservation and cultivation of threatened and high valued medicinal plants in North East India. International Journal of Biodiversity and Conservation. 2013 Sep 30;5(9):584-91.

39) Mao A A&Hynniewta T M, Floristic diversity of North East India, J Assam SciSoc, 41(4) (2000) 255-26.

40) Mao AA, Hynniewta TM, Sanjappa M. Plant wealth of Northeast India with reference to ethnobotany. Indian journal of traditional knowledge. 2009 Jan 1;8(1):96-103.

41) Sharma UK. PLANTS USED FOR ETHNOMEDICINE BY THE NEPALESE OF ASSAM, INDIA. In Ethnobiology and conservation of cultural and biological diversity: proceedings of the Fifth International Congress of Ethnobiology, Nairobi, Kenya, September 2-6 1996 2002 (p. 83). National Museums of Kenya.

42) Karki H, Upadhayay K, Pal H, Singh R. Antidiabetic potential of Zanthoxylum armatum bark extract on streptozotocin-induced diabetic rats. International Journal of Green Pharmacy (IJGP). 2014;8(2).

43) Sati SC, Sati MD, Raturi R, Badoni P, Singh H. Anti-inflammatory and antioxidant activities of Zanthoxylum armatum stem bark. Global Journal of researches in engineering: J General Engineering. 2011 Jul;5:86.

44) Antinociceptive and anti-inflammatory activities of ethyl acetate fraction from Zanthoxylum armatum in mice. Fitoterapia. 2011 Apr 30;82(3):347-51.

45) Sharma, A., G.S. Joseph, and R.P. Singh, Antioxidant and antiplatlet aggregation properties of bark extracts of Garcinia pedunculata and Garcinia cowa. Journal of food science and technology. 51(8): p. 1626-1631.

46) Sarma, R., et al., Polyphenol rich extract of Garcinia pedunculata fruit attenuates the hyperlipidemia induced by high fat diet. Frontiers in pharmacology. 7.

47) Negi, P.S., G.K. Jayaprakasha, and B.S. Jena, Antibacterial activity of the extracts from the fruit rinds of Garcinia cowa and Garcinia pedunculata against food borne pathogens and spoilage bacteria. LWT-Food Science and Technology, 2008. 41(10): p. 1857-1861.

48) Ruma, K., S. Kumar, and H.S. Prakash, Antioxidant, anti-inflammatory, antimicrobial and cytotoxic properties of fungal endophytes from Garcinia species. International Journal of Pharmacy and Pharmaceutical Sciences. 5(3): p. 889-897.

49) Mundugaru, R., M. Chakkravarthy, and R. Basavaiah, Hepatoprotective activity of fruit extract garcinia pedunculata. Bangladesh Journal of Pharmacology. 9(4): p. 483-487.

50) Mundugaru, R., et al., Cardioprotective activity of fruit of garcinia pedunculata on isoprenaline-induced myocardial infarction in rat. Bangladesh Journal of Pharmacology. 11(1): p. 231-235.

51) Sharma, P.B., P.J. Handique, and H.S. Devi, Antioxidant properties, physico-chemical characteristics and proximate composition of five wild fruits of Manipur, India. Journal of food science and technology. 52(2): p. 894-902.

52) Hullatti, K.K. & Rai, V.R. Antimicrobial activity of Memecylon malabaricum leaves. Fitoterapia 75, 409-411 (2004).

53) Aparna Areti, Dinesh Tummuri, ganesh Yerra, Asutosh Kumar, VGM Naidu*, Boswellia ovalifoliolata abrogates ROS mediated NF-kB activation, causes apoptosis and chemosensitization in Triple Negative Breast Cancer cells. Environmental Toxicology and Pharmacology. (Under review, Manuscript ID: ETAP-D-13-00447).

54) Ethanolic extract of Boswellia ovalifoliolata bark and leaf attenuates doxorubicin-induced cardiotoxicity in mice. Bandari Uma Mahesh, Shweta Shrivastava, Madhusudhana Kuncha, Bidya Dhar Sahu, Challa Veerabhadra Swamy, Rajeswara Rao Pragada, V.G.M. Naidu, Ramakrishna Sistla. Environmental Toxicology and Pharmacology, 2013 In Press.

55) Karki, H., et al., Antidiabetic potential of Zanthoxylum armatum bark extract on streptozotocin-induced diabetic rats. International Journal of Green Pharmacy (IJGP), 2014. 8(2).

56) Sati, S., et al., Anti-inflammatory and antioxidant activities of Zanthoxylum armatum stem bark. Global Journal of researches in engineering: J General Engineering, 2011. 5: p. 86.

57) Guo, T., et al., Antinociceptive and anti-inflammatory activities of ethyl acetate fraction from Zanthoxylum armatum in mice. Fitoterapia, 2011. 82(3): p. 347-351.

58) Sharma, A., G. Joseph, and R. Singh, Antioxidant and antiplatlet aggregation properties of bark extracts of Garcinia pedunculata and Garcinia cowa. Journal of food science and technology, 2014. 51(8): p. 1626-1631.

59) Sarma, R., et al., Polyphenol rich extract of Garcinia pedunculata fruit attenuates the hyperlipidemia induced by high fat diet. Frontiers in Pharmacology, 2016. 7: p. 294.

60) Negi, P., G. Jayaprakasha, and B. Jena, Antibacterial activity of the extracts from the fruit rinds of Garcinia cowa and Garcinia pedunculata against food borne pathogens and spoilage bacteria. LWT-Food Science and Technology, 2008. 41(10): p. 1857-1861.

61) Ruma, K., K. Sunil, and H. Prakash, Antioxidant, anti-inflammatory, antimicrobial and cytotoxic properties of fungal endophytes from Garcinia species. Int J Pharm Pharm Sci, 2013. 5(3): p. 889-897.

62) Mundugaru, R., M.C. Varadharajan, and R. Basavaiah, Hepatoprotective activity of fruit extract of Garcinia pedunculata. ||| Bangladesh Journal of Pharmacology, 2014. 9(4): p. 483-87.

63) Mundugaru, R., et al., Cardioprotective activity of fruit of garcinia pedunculata on isoprenaline-induced myocardial infarction in rat. ||| Bangladesh Journal of Pharmacology, 2016. 11(1): p. 231-235.

64) Sharma, P.B., P.J. Handique, and H.S. Devi, Antioxidant properties, physico-chemical characteristics and proximate composition of five wild fruits of Manipur, India. Journal of food science and technology, 2015. 52(2): p. 894-902

65) Stewart, B. and C.P. Wild, World cancer report (2014). World.

66) Parkin, D.M., et al., Estimating the world cancer burden: Globocan (2000). International journal of cancer, 2001. 94.2: (153-156).

67) Jemal, A., et al., Global cancer statistics. CA: a cancer journal for clinicians (2015);

61.2:(69-90).

68) Huang, E.S. Internal medicine: handbook for clinicians, resident survival guide. Arlington, VA: Scrub Hill Press (2000); p.130.

69) Salvayre, A.N, Dousset, N., Ferretti, G., Bacchetti, T., Curatola, G. and Salvayre, R.

Antioxidant and cytoprotective properties of high-density lipoproteins in vascular cells. Free Radic Biol Med (2006); 41.7: 1031-1040.

70) Chowdhuri SK: From Ethnobotany. In Studies in Botany Volume 2. 7th edition. Edited by: Mitra D, Guha J. Chowdhuri SK, Kolkata: Manasi Press; 2000:(855-867)

71) Kumar, D., et al., Anti-leukemic activity of Dillenia indica L. fruit extract and quantification of betulinic acid by HPLC. Phytomedicine (2009) 17(6): p. 431-435

72) Kumar, S., V. Kumar, and O. Prakash, Antidiabetic, hypolipidemic and histopathological analysis of Dillenia indica (L.) leaves extract on alloxan induced diabetic rats. Asian Pacific journal of tropical medicine. 4(5): p. 347-352.

73) Apu, A.S., et al., Antimicrobial Activity and Brine Shrimp Lethality Bioassay of the Leaves Extract of Dillenia indica Linn. Journal of Young Pharmacists. 2(1): p. 50-53.

74) Rai, P.K. and H. Lalramnghinglova, Ethnomedicinal plant resources of Mizoram, India: Implication of traditional knowledge in health care system. Ethnobotanical Leaflets. 2010(3): p. 6.

75) Akter, R., et al., Cytotoxic activity screening of Bangladeshi medicinal plant extracts. Journal of natural medicines. 68(1): p. 246-252.

76) Saiful Yazan, L. and N. Armania, Dillenia species: A review of the traditional uses, active constituents and pharmacological properties from pre-clinical studies. Pharmaceutical biology. 52(7): p. 890-897.

77) Alam, M.B., et al., Antinociceptive and antioxidant activities of the Dillenia indica bark. international Journal of Pharmacology. 8(4): p. 243-251

78) Ashish KS, antibacterial, anti-alpha glucosidase and antioxidant properties of Dillenia pentagyna Asian journal of pharmaceutical & clinical Research (2013)

79) Barreira, J. o., Ferreira, I. C. F. R., Oliveira, M., & Pereira, J. A. (2008). Antioxidant activities of the extracts from chestnut flower, leaf, skins and fruit. Food Chemistry, 107(3), 1106-1113

80) Marwah, R. G., Fatope, M. O., Mahrooqi, R. A., Varma, G. B., Abadi, H. A., & Al-Burtamani, S. K. S. (2007). Antioxidant capacity of some edible and wound healing plants in Oman. Food Chemistry, 101(2), 465-470.

81) Olabinri, B. M., Odedire, O. O., Olaleye, M. T., Adekunle, A. S., Ehigie, L. O., & Olabinri, P. F. (2010). In vitro evaluation of hydroxyl and nitric oxide radical scavenging activities of Artemether. Research Journal of Biological Sciences, 5(1), 102-105.

82) Riccardi et al. Analysis of apoptosis by propidium iodide staining and flow cytometry.Nat protoc (2006);1:(1458–1461)

83) Kumar, Vikas, Santosh K. Guru, Shreyans K. Jain, Prashant Joshi, Sumit G. Gandhi, Sandip B. Bharate, Shashi Bhushan, Sonali S. Bharate, and Ram A. Vishwakarma. Bioorganic & medicinal chemistry letters 26, no. 15 (2016): 3457-3463.

84) Lakdawala, A. D., M. V. Shirole, S. S. Mandrekar, and A. N. Dohadwalla. Asia Pacific Journal of Pharmacology 3, no. 2 (1988): 91-98.

85) Chhonker, Yashpal S., Hardik Chandasana, Ashok Kumar, Deepak Kumar, Tulsankar Sachin Laxman, Sunil Kr Mishra, Vishal M. Balaramnavar, Shishir Srivastava, Anil K. Saxena, and Rabi S. Bhatta. Drug research 65, no. 07 (2015): 380-387.

86) Niaz, K.; Maqbool, F.; Khan, F.; Bahadar, H.; Hassan, F. I.; Abdollahi, M., Smokeless tobacco (paan and gutkha) consumption, prevalence, and contribution to oral cancer. Epidemiology and health 2017, 39.

87) Wynder, E. L.; Bross, I. J.; Feldman, R. M., A study of the etiological factors in cancer of the mouth. Cancer 1957, 10 (6), 1300-1323.

88) Lawoyin, J.; Lawoyin, D.; Aderinokun, G., Intra-oral squamous cell carcinoma in Ibadan: a review of 90 cases. TROPICAL DENTAL JOURNAL 1996, 12-15.

89) Kulkarni, M. R., Head and neck cancer burden in India. Int J Head Neck Surg 2013, 4 (1), 29-35.

90) Cooper, J. S.; Fu, K.; Marks, J.; Silverman, S., Late effects of radiation therapy in the head and neck region. International Journal of Radiation Oncology* Biology* Physics 1995, 31 (5), 1141-1164.

91) Gorenc, M.; Kozjek, N. R.; Strojan, P., Malnutrition and cachexia in patients with head and neck cancer treated with (chemo) radiotherapy. Reports of Practical Oncology & Radiotherapy 2015, 20 (4), 249-258.

92) Nyst, H. J.; Tan, I. B.; Stewart, F. A.; Balm, A. J., Is photodynamic therapy a good alternative to surgery and radiotherapy in the treatment of head and neck cancer? Photodiagnosis and photodynamic therapy 2009, 6 (1), 3-11.

93) Chang, H.-P.; Sheen, L.-Y.; Lei, Y.-P., The protective role of carotenoids and polyphenols in patients with head and neck cancer. Journal of the Chinese Medical Association 2015, 78 (2), 89-95.

94) Nishimuro, H.; Ohnishi, H.; Sato, M.; Ohnishi-Kameyama, M.; Matsunaga, I.; Naito, S.; Ippoushi, K.; Oike, H.; Nagata, T.; Akasaka, H., Estimated daily intake and seasonal food sources of quercetin in Japan. Nutrients 2015, 7 (4), 2345-2358.

95) Chen, S.-F.; Nien, S.; Wu, C.-H.; Liu, C.-L.; Chang, Y.-C.; Lin, Y.-S., Reappraisal of the anticancer efficacy of quercetin in oral cancer cells. Journal of the Chinese Medical Association 2013, 76 (3), 146-152.

96) Lai, W.-W.; Hsu, S.-C.; Chueh, F.-S.; Chen, Y.-Y.; Yang, J.-S.; Lin, J.-P.; Lien, J.-C.; Tsai, C.-H.; Chung, J.-G., Quercetin inhibits migration and invasion of SAS human oral cancer cells through inhibition of NF-κB and matrix metalloproteinase-2/-9 signaling pathways. Anticancer research 2013, 33 (5), 1941-1950.

97) Ma, Y. S.; Yao, C. N.; Liu, H. C.; Yu, F. S.; Lin, J. J.; Lu, K. W.; Liao, C. L.; Chueh, F. S.; Chung, J. G., Quercetin induced apoptosis of human oral cancer SAS cells through mitochondria and endoplasmic reticulum mediated signaling pathways. Oncology letters 2018, 15 (6), 9663-9672.

98) Zhang, C.; Hao, Y.; Sun, Y.; Liu, P., Quercetin suppresses the tumorigenesis of oral squamous cell carcinoma by regulating microRNA-22/WNT1/β-catenin axis. Journal of Pharmacological Sciences 2019.

99) Srinivasan, K., Black pepper and its pungent principle-piperine: a review of diverse physiological effects. Critical reviews in food science and nutrition 2007, 47 (8), 735-748.

100) Siddiqui, S.; Ahamad, M. S.; Jafri, A.; Afzal, M.; Arshad, M., Piperine triggers apoptosis of human oral squamous carcinoma through cell cycle arrest and mitochondrial oxidative stress. Nutrition and cancer 2017, 69 (5), 791-799.

101) Khajuria, A.; Zutshi, U.; Bedi, K., Permeability characteristics of piperine on oral absorption-an active alkaloid from peppers and a bioavailability enhancer. Indian journal of experimental biology 1998, 36, 46-50.

102) Rather, R. A.; Bhagat, M., Cancer chemoprevention and piperine: Molecular mechanisms and therapeutic opportunities. Frontiers in cell and developmental biology 2018, 6, 10.

103) Atal, N.; Bedi, K., Bioenhancers: Revolutionary concept to market. Journal of Ayurveda and integrative medicine 2010, 1 (2), 96.

104) Gorgani, L.; Mohammadi, M.; Najafpour, G. D.; Nikzad, M., Piperine—the bioactive compound of black pepper: from isolation to medicinal formulations. Comprehensive Reviews in Food Science and Food Safety 2017, 16 (1), 124-140.

105) Chaudhari, V. S.; Hazam, P. K.; Banerjee, S., Lipid Nanoarchitectonics for Natural Products Delivery in Cancer Therapy. In Sustainable Agriculture Reviews 44, Springer: 2020; pp 169-203.

106) Kazusaki, M.; Ueda, S.; Takeuchi, N.; Ohgami, Y., Validation of analytical procedures by high− performance liquid chromatography for pharmaceutical analysis. Chromatography 2012, 33 (2), 65-73.

107) Sanghavi, N.; Bhosale, S.; Malode, Y.; Sanghavi, N., RP-HPLC method development and validation of Quercetin isolated from the plant Tridax procumbens L. J Sci Innov Res 2014, 3 (6), 594-597.

108) Quijia, C. R.; Chorilli, M., Characteristics, biological properties and analytical methods of piperine: a review. Critical reviews in analytical chemistry 2019, 1-16.

109) Aneja, G.; Dave, U.; Vadodaria, K., Simultaneous Estimation of Piperine, Quercetin and Curcumin in A Mixture Using UV-Visible Spectrophotometer and Method Validation. IJTA 2012, 8, 14-7.

110) Amidon, G. L.; Lennernäs, H.; Shah, V. P.; Crison, J. R., A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharmaceutical research 1995, 12 (3), 413-420.

111) Dall'Acqua, S.; Miolo, G.; Innocenti, G.; Caffieri, S., The photodegradation of quercetin: relation to oxidation. Molecules 2012, 17 (8), 8898-8907.

112) Cai, X.; Fang, Z.; Dou, J.; Yu, A.; Zhai, G., Bioavailability of quercetin: problems and promises. Current medicinal chemistry 2013, 20 (20), 2572-2582.

113) Shao, B.; Cui, C.; Ji, H.; Tang, J.; Wang, Z.; Liu, H.; Qin, M.; Li, X.; Wu, L., Enhanced oral bioavailability of piperine by self-emulsifying drug delivery systems: in vitro, in vivo and in situ intestinal permeability studies. Drug delivery 2015, 22 (6), 740-747.

114) Muchow, M.; Maincent, P.; Müller, R. H., Lipid nanoparticles with a solid matrix (SLN®, NLC®, LDC®) for oral drug delivery. Drug development and industrial pharmacy 2008, 34 (12), 1394-1405.

115) Das, S.; Chaudhury, A., Recent advances in lipid nanoparticle formulations with solid matrix for oral drug delivery. AAPS PharmSciTech 2011, 12 (1), 62-76.

116) Chen-yu, G.; Chun-fen, Y.; Qi-lu, L.; Qi, T.; Yan-wei, X.; Wei-na, L.; Guang-xi, Z., Development of a quercetin-loaded nanostructured lipid carrier formulation for topical delivery. International journal of pharmaceutics 2012, 430 (1-2), 292-298.

117) Li, Q.; Cai, T.; Huang, Y.; Xia, X.; Cole, S. P.; Cai, Y., A review of the structure, preparation, and application of NLCs, PNPs, and PLNs. Nanomaterials 2017, 7 (6), 122.

118) Mehnert, W.; Mäder, K., Solid lipid nanoparticles: production, characterization and applications. Advanced drug delivery reviews 2012, 64, 83-101.

119) Natarajan, J.; Karri, V.; Anindita, D., Nanostructured lipid carrier (NLC): a promising drug delivery system. Global Journal of Nanomedicine 2017, 1 (5), 001-006; (b) Khan, S.; Baboota, S.; Ali, J.; Khan, S.; Narang, R. S.; Narang, J. K., Nanostructured lipid carriers: An emerging platform for improving oral bioavailability of lipophilic drugs. International journal of pharmaceutical investigation 2015, 5 (4), 182.

120) Das, S.; Ng, W. K.; Tan, R. B., Are nanostructured lipid carriers (NLCs) better than solid lipid nanoparticles (SLNs): development, characterizations and comparative evaluations of clotrimazole-loaded SLNs and NLCs? European journal of pharmaceutical sciences 2012, 47 (1), 139-151.

121) Iqbal, M. A.; Md, S.; Sahni, J. K.; Baboota, S.; Dang, S.; Ali, J., Nanostructured lipid carriers system: recent advances in drug delivery. Journal of drug targeting 2012, 20 (10), 813-830.

122) Graves, R. A.; Ledet, G. A.; Nation, C. A.; Pramar, Y. V.; Bostanian, L. A.; Mandal, T. K., Effect of squalane on mebendazole-loaded Compritol® nanoparticles. Journal of Biomaterials Science, Polymer Edition 2015, 26 (13), 868-880.

123) Banerjee, S.; Roy, S.; Nath Bhaumik, K.; Kshetrapal, P.; Pillai, J., Comparative study of oral lipid nanoparticle formulations (LNFs) for chemical stabilization of antitubercular drugs: physicochemical and cellular evaluation. Artificial cells, nanomedicine, and biotechnology 2018, 46 (sup1), 540-558.

124) Teeranachaideekul, V.; Souto, E. B.; Müller, R. H.; Junyaprasert, V. B., Physicochemical characterization and in vitro release studies of ascorbyl palmitate-loaded semi-solid nanostructured lipid carriers (NLC gels). Journal of microencapsulation 2008, 25 (2), 111-120.

125) Banerjee, S.; Roy, S.; Bhaumik, K. N.; Pillai, J., Mechanisms of the effectiveness of lipid nanoparticle formulations loaded with anti-tubercular drugs combinations toward overcoming drug bioavailability in tuberculosis. Journal of Drug Targeting 2020, 28 (1), 55-69.

126) Yoon, G.; Park, J. W.; Yoon, I.-S., Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs): recent advances in drug delivery. Journal of Pharmaceutical Investigation 2013, 43 (5), 353-362.

127) Moreno-Bautista, G.; Tam, K. C., Evaluation of dialysis membrane process for quantifying the in vitro drug-release from colloidal drug carriers. Colloids and Surfaces A: Physicochemical and Engineering Aspects 2011, 389 (1-3), 299-303.

128) Bose, S.; Michniak-Kohn, B., Preparation and characterization of lipid based nanosystems for topical delivery of quercetin. European Journal of Pharmaceutical Sciences 2013, 48 (3), 442-452.

129) Wyatt, D., Taking poorly water soluble compounds through discovery. Bulletin technique-Gattefossé report 1999, (92), 31-39.

130) Higuchi, T., Rate of release of medicaments from ointment bases containing drugs in suspension. Journal of pharmaceutical sciences 1961, 50 (10), 874-875.

131) Ramteke, K.; Dighe, P.; Kharat, A.; Patil, S., Mathematical models of drug dissolution: a review. Sch. Acad. J. Pharm 2014, 3 (5), 388-396.

132) Dobrovolskaia, M. A.; Clogston, J. D.; Neun, B. W.; Hall, J. B.; Patri, A. K.; McNeil, S. E., Method for analysis of nanoparticle hemolytic properties in vitro. Nano letters 2008, 8 (8), 2180-2187.

133) Lopes, R.; Eleutério, C.; Gonçalves, L.; Cruz, M.; Almeida, A., Lipid nanoparticles containing oryzalin for the treatment of leishmaniasis. European Journal of Pharmaceutical Sciences 2012, 45 (4), 442-450.

134) Suhitha, Sivasubramanian, Seenivasan K. Devi, Krishnasamy Gunasekaran, H. Carehome Pakyntein, Atanu Bhattacharjee, and Devadasan Velmurugan. "Phytochemical analyses and activity of herbal medicinal plants of North-East India for anti-diabetic, anti-cancer and anti-tuberculosis and their docking studies." Current topics in medicinal chemistry 15, no. 1 (2015): 21-36.

135) Singh, Garima, Ajit K. Passsari, Vincent V. Leo, Vineet K. Mishra, Sarathbabu Subbarayan, Bhim P. Singh, Brijesh Kumar et al. "Evaluation of phenolic content variability along with antioxidant, antimicrobial, and cytotoxic potential of selected traditional medicinal plants from India." Frontiers in plant science 7 (2016): 407.

136) Tariq, Akash, Sakina Mussarat, and Muhammad Adnan. "Review on ethnomedicinal, phytochemical and pharmacological evidence of Himalayan anticancer plants." Journal of ethnopharmacology 164 (2015): 96-119.

8 ACKNOWLEDGEMENTS

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APPENDICES

Appendix 1 – Details of Technical Activities
Appendix 2 – Copies of Publications duly Acknowledging the Grant/ Fund Support of NMHS
Appendix 3 – List of Trainings/ Workshops/ Seminars with details of trained resources and dissemination material and Proceedings
Appendix 4 – List of New Products (utilizing the local produce like NTFPs, wild edibles, bamboo, etc.)
Appendix 5 – Copies of the Manual of Standard Operating Procedures (SOPs) developed
Appendix 6 – Details of Technology Developed/ Patents filed
Appendix 7 – Any other (specify)

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(Signature of HRA/HJRF/HPF)

(NMHS FELLOWSHIP COORDINATOR)

(Signed and Stamped)

(HEAD OF THE INSTITUTION)

(Signed and Stamped)

Place: .....
Date: ...../...../.....

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