



# HAMSA HOMEOPATHY

## Medical College, Hospital & Research Centre

Opp. ZPHS, Ksheerasagar (V), Mulugu (M), Siddipet (Dt.) - 502279, Telangana, INDIA.

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Ref: H HMCH/EMR/19/247

Ksheerasagar  
Date: 30/12/2019

To  
The Director General  
Central Council for Research in Homeopathy,  
Janakpuri, New Delhi – 110023

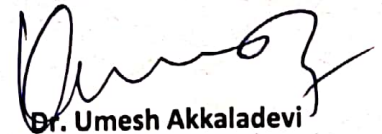
Dear Sir,

Sub: Resubmission of the proposal after the corrections for Extra Mural Research Project (EMR) Scheme, regarding  
Ref: File Number: 23-119/2019-20/CCRH/TECH/EMR

I, Dr. Umesh Akkaladevi, Director & Medical Superintendent, Hamsa Homeopathy Medical College, Hospital & Research Centre located at Ksheerasagar Village, Mulugu Mandal, Siddipet Dist., Telangana, am herewith attaching the corrected proposal along with reply to your comments mentioned in the reference above. I request you to kindly accept and acknowledge the receipt of the same and consider for Research Project under EMR Scheme.

Thank you

Yours sincerely

  
Dr. Umesh Akkaladevi



File Number:23-119/2019-20/CCRH/TECH/EMR

Project Title: Effect of Arsenicum album a homoeopathic drug on JAK-STAT pathway in the management of irritable bowel syndrome (IBS)

PI Name: Dr Manjula Bhanoori, University College of Science, Osmania University, Hyderabad

### 1. Comments on Objectives

Does the proposal address well-defined scientific questions? Is it focused?

- Not focused

Yes, it is focused. The proposal addresses a well-defined scientific reasoning which is study of the effects of a homoeopathic drug on an inflammatory process involving JAK and STAT proteins at the molecular level. The preliminary work has been carried out in the Dept. of Biochemistry, Osmania University under the guidance of the Principal Investigator.

### 2. Scientific/Technical merit of the proposal

Will the research enhance our understanding of the problem being studied? What is the perceived impact of the proposed research?

- Poorly conceptualized. How JK STAT, Irritable Bowel Disease and IBS & Homoeopathy are related?

Inflammation of the gastrointestinal tract is the hallmark of inflammatory bowel disease. The Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway modulates the inflammation induced by several cytokines. This signaling pathway has been implicated in the pathogenesis of inflammatory bowel disease (IBD). Recently JAK/STAT pathway is receiving increasing attention as a novel target for therapeutic intervention and inhibitors of the pathway are now considered as innovative third generation therapeutic agents for IBD. Tofacitinib is a janus kinase inhibitor used to treat ulcerative colitis and is the first jakinib (janus kinase inhibitor) to be approved by the US Food and Drug Administration (FDA) in May 2018. Arsenicum Album (arsenic trioxide) is a homeopathic medicine used for the treatment of inflammatory diseases of the GI system. Recent research showed Arsenic trioxide at the concentration of 10  $\mu$ M inhibits JAK/STAT pathway but the mechanism of action of arsenic at very low concentrations used in homeopathy is not well understood. The focus of the present proposal is to decipher the mechanism of action of arsenic trioxide at homeopathic potencies (1X to 200X) in the treatment of IBD with respect to JAK/STAT pathway.

### 3. Comments on work plan, methodology and time schedule

Do you think the work plan and methodology proposed against each of the objectives are appropriate? Will they lead to successful outcome?

- Topic is on Irritable bowel syndrome. Citation is on Inflammatory Bowel syndrome. Part of methodology is in past tense. It is not clear what work has already been completed? From whom samples has been collected?

Focus of the proposal is Inflammatory Bowel Disease (IBD) and in the modified version of the proposal Irritable bowel syndrome (IBS) in the title is corrected as IBD. The research topic is on Inflammation and the proposed research work is on a homoeopathic drug on Inflammatory Bowel Disease (IBD) which will pave a way to understand the pathological effects of ultra dilutions which in turn will pave a way to address many non-communicable diseases. Arsenicum album usage is considered effective in treating

inflammation of the mucus membranes and is a commonly indicated therapeutic drug in many cases of Inflammatory Bowel Disease. Hence, the study here is inflammatory bowel disease (IBD). Studies on JAK-STAT pathway have already been completed and published by the Principal Investigator (PI) at the cellular level. The past tense in part of the methodology is corrected in the modified version of the proposal .

#### 4. Budget viability (with changes sought if any)

Can the proposed research be accomplished with requested budget and within the time frame? Is the budget too ambitious or too little? Are the equipment proposed vital or the PIs can use the equipment available in the departments/institutions?

- Salary is high, no justification is given. Books, equipments no details given.

Salaries are quoted according to ICMR guidelines for a period of 2 years. Justification of salaries, books and equipment details is being attached.

#### 5. Any other comments for the benefit of the PI(s)

- PI is from Osmania University, Co-I is from Hamsa Homoeopathy Medical College & another Co-I is from Gandhi Medical college, Secunderabad. Head of the institute is from Co-I institute? Study site is not clear and role of PI/Co-I is not clear.

PI is from Osmania University who has expertise in molecular work and she is well versed with JAK-STAT pathway with numerous publications. The molecular work of this study will be done by PI at Osmania University. Co-Investigator-I is a homeopathic practitioner and also the head of the institution who will assist the PI in studying the effect of Arsenicum album, a homeopathic drug in different potencies, on JAK-STAT pathway at the molecular level. The samples specific to Inflammatory Bowel Disease will be collected from patients attending the OPD/IPD of Hamsa Homeopathy Medical College, Hospital & Research Centre (HHMCHRC). The required samples of Arsenicum album in different potencies will be supplied by HHMCHRC and the effects will be studied, again at the molecular level. The working staff such as RA, SRF, JRF, Lab Assistants, etc. will be appointed by Dept of Biochemistry, Osmania University and HHMCHRC. Co-investigator-II is from Gandhi Medical College working as Scientist II in Multi-Disciplinary Research Unit (MDRU) will assist in molecular work .

## Section – C

### **BRIEF SUMMARY OF THE RESEARCH PROPOSAL**

#### **1. Title of the Research Project:**

**Effect of Arsenicum album, a homeopathic drug, on JAK-STAT pathway in the Management of Inflammatory Bowel Disease (IBD)**

#### **2. Objectives:**

1. Analysis of Arsenic presence in homeopathic drug potencies by bio-physical methods
2. To study the effect of Arsenicum album (different potencies) on JAK-STAT pathway in cases of Inflammatory Bowel Disease
3. To study the effect of Arsenicum album (different potencies) on cell proliferation and Apoptosis

#### **3. Methodology:**

- a. Biophysical Methods
- b. Western Blot Technique / Immunoblotting Assay
- c. MTT Assay

#### **4. Anticipated Outcome:**

- The Law of Similars of Homoeopathy can be verified by studying the poisonous effects and the therapeutic effects of Arsenicum album in Q and different potencies.
- Effects of homoeopathic drugs in potentized form at the cellular level with a biotechnological method which could be used to evaluate the physiological effects of homoeopathic potencies on human cells.
- Probability of finding a cure for Inflammatory Bowel Disease and thereby for many other inflammatory diseases.

#### **5. Summary of the proposed research:**

Homoeopathy, though born in Germany, is drawing a lot of patients in the recent times in India due to the fact that the Government of India under AYUSH Ministry is encouraging alternative systems of medicine. There is a need for a scientific answer to the intriguing question about the action of homeopathic drugs through research. This is possible only if the drugs are validated through an exhaustive research process based on standard parameters. Therefore, Hamsa Homeopathy Medical College, Hospital & Research Centre has resolved to take up this herculean task of conducting extensive research in the areas less touched – Immunological Action of Homeopathic Medicines at the “cell level”.

For this, we are collaborating with Dr. Manjula Bhanoori, Ph.D., Dept. of Biochemistry, a senior scientist and Asst. Professor in the University College of Science, Osmania University, Hyderabad and Dr. Madhavalatha, Ph.D., a Research Scientist at Gandhi Medical College, Hyderabad, to take up this project - **Effect of Arsenicum album, a homeopathic drug, on JAK-STAT pathway in the management of Inflammatory Bowel Disease (IBD)** which will further pave a way to address many other Non-communicable Diseases.

**6. IPR Values: Not Assessed**

**7. Translational Value:**

This study will be highly useful in medicine to find an alternative option for difficult-to-cure diseases like Inflammatory Bowel Disease.

**8. Utilization of outcomes of project:**

Various Homoeopathic drugs can be studied on different pathways (JAK-STATS), which is mainly concerned with immunity.

## SECTION – D

### Detailed Research Protocol

#### **Introduction:**

Arsenicum album is one of the most important and frequently-used homeopathic remedies prepared from a substance supposedly derived from the metallic element Arsenic. It is used to treat a range of symptoms that include digestive disorders especially food poisoning, allergies, anxiety, depression and obsessive-compulsive disorder. It has been studied as a possible treatment for arsenic poisoning. Arsenicum album usage is considered effective in treating conditions that are aggravated by cold, dry, windy weather; conditions such as asthma, inflamed eyes that water and sting, headaches with vomiting and dizziness, **inflammation of the mucous membranes** and mouth ulcers and ailments characterized by burning pain. It is also utilized for fevers that are accompanied by chills. The arsenic oxide in a homeopathic preparation is highly diluted, and so is considered generally safe, although rare reports of arsenic poisoning from poorly-prepared homeopathic treatments sold in India have been reported. When properly prepared, however, the extreme dilutions, typically to at least 1 in  $10^{24}$ , or 12C in homeopathic notation, mean that it is extremely statistically unlikely that any pill contains even a molecule of the original arsenic used. While some small, unblinded studies have claimed an effect on reducing arsenic toxicity, they do not recommend its large-scale use, and studies of homeopathic remedies have shown to generally have problems that prevent them from being considered unambiguous evidence. There is no known mechanism for how Arsenicum album could remove arsenic from the body, and there is insufficient evidence for it to be considered effective medicine (for any condition) by the scientific community.

#### **Relevance and usefulness of the study with particular reference to Homeopathic system:**

Homeopathy is based on the law of similars. This law states that there is a parallel action between the power of a substance and its therapeutic action. Put in more pedestrian terms, the same things that cause the disease can cure it. Homeopathic studies are known to have problems, such as evidence of bias, lack of rigour, and failure to blind the experimenters or subjects to which group is being analysed that prevent them from being considered definitive evidence for any effect. The ideas behind homeopathy are scientifically implausible and directly opposed to fundamental principles of natural science and modern medicine, which means that poorly-conducted, small, or unblinded studies are not considered scientific proof of efficacy. Conventional scientific wisdom dictates that homeopathy should have no effect above placebo but experiments on ultra-high dilutions of solutes together with some clinical data suggest the intriguing possibility that it might do in some circumstances.

The Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway is an essential cascade for mediating normal functions of different cytokines in the development of the hematopoietic and immune systems. Recent studies, both cell culture and animal models showed evidence that arsenic negatively regulates this pathway and thus influences the immunity and inflammatory responses.

Taking into consideration the role of arsenic as a homeopathic drug, which plays a role in immunity, and basic research showing it as a negative regulator of JAK-STAT pathway and thus in immunity and inflammation, we propose to study the role of arsenicum album (different potencies) in the regulation of JAK-STAT pathway using cell culture strategy.

The homeopathic mode of treatment often encourages use of drugs at such ultra-low doses and high dilutions that even the physical existence of a single molecule of the original drug substance becomes theoretically impossible. But homeopathy has sustained for over two hundred years despite periodical challenges thrown by scientists and non-believers regarding its scientificity. There has been a spurt of research activities on homeopathy in recent years, at clinical, physical, chemical, biological and medical levels with acceptable scientific norms and approach. While clinical effects of some homeopathic drugs could be convincingly shown, one of the greatest objections to this science lies in its inability to explain the mechanism of action of the microdoses based on scientific experimentations and proofs. Though many aspects of the mechanism of action still remain unclear, serious efforts have now been made to understand the molecular mechanism(s) of biological responses to the potentized form of homeopathic drugs.

#### **Interdisciplinary relevance:**

Basic cell biology and biochemistry research can validate the action and efficacy of drugs used in homeopathy.

#### **Review of Research and Development in the Subject:**

Arsenicum album is shown to be protective against chronic arsenic poisoning in mice model experiments, ameliorative potential against arsenic toxicity was also indicated in pilot studies using human subjects. Arsenic showed a significant stimulating effect on seedling growth in the wheat germination model. In plant based bioassays arsenic treatment imparted resistance to tobacco mosaic virus. The Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway is an essential cascade for mediating normal functions of different cytokines in the development of the hematopoietic and immune systems. Chronic exposure to arsenic has been found to cause immunotoxicity and has been associated with the suppression of hematopoiesis (anemia and leukopenia). Arsenic-mediated inactivation of the JAK-STAT signaling pathway by its direct interaction with JAK tyrosine kinase has been reported.

#### **Citations**

- **Involvement of JAK/STAT signaling in the pathogenesis of inflammatory bowel disease.**

Pharmacol Res. 2013 Oct;76:1-8. doi: 10.1016/j.phrs.2013.06.007. Epub 2013 Jul 2.

Coskun M(1), Salem M, Pedersen J, Nielsen OH.

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The Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway constitute the fulcrum in many vital cellular processes, including cell growth, differentiation, proliferation, and regulatory immune functions. Various cytokines, growth factors, and protein tyrosine kinases communicate through the JAK/STAT pathway and regulate the transcription of numerous genes. In addition to their critical roles in a plethora of key cellular activities, the JAK/STAT signalling pathways also have been implicated in the pathogenesis of several diseases, including inflammatory bowel disease (IBD), especially since a JAK inhibitor recently has been shown to be effective in the treatment of ulcerative colitis. The aim of this review is to highlight the recent findings on the regulatory mechanism of JAK/STAT signaling pathways and to reveal the evolving comprehension of their interface which might be of interest for clinicians involved in IBD therapy. Further, it is described how these signalling pathways have been exploited for the development of promising novel JAK inhibitors with anti-inflammatory effects verified in clinical trials.

- **Arsenic Inhibits the JAK-STAT Signaling Pathway**

Biochempages August 27, 2015

Arsenic is a toxic element that affects the normal cellular processes. Arsenic causes poisoning of the glycolysis and TCA cycle by inhibiting their key enzymes while it also suppresses the hematopoietic and immune system as well as it is also associated with cancer. The ability of arsenic to suppress the hematopoiesis and to induce the immunotoxicity on different immune cells suggests that arsenic and its compounds (arsenicals) may involve the inhibition of the cytokine receptors and their downstream signaling pathways.

- **"Do We Know Jack" About JAK? A Closer Look at JAK/STAT Signaling Pathway**

Emira Bousoik 1,2 and Hamidreza Montazeri Aliabadi 1\*

1 Department of Biomedical and Pharmaceutical Sciences, Center for Targeted Drug Delivery, School of Pharmacy, Chapman University, Irvine, CA, United States

2 School of Pharmacy, Omar Al-Mukhtar University, Dèrna, Libya

Front. Oncol., 31 July 2018 | <https://doi.org/10.3389/fonc.2018.00287>

Cytokine receptors activate JAK/STAT pathway through a variety of combinations of different JAK and STAT family members, which highlights the versatile nature of this pathway. The receptors in this family that are linked to JAK activation could be categorized as interleukin (IL) receptors, Interferon (IFN) receptors, and colony stimulating factor receptors (CSFRs). In mammals, the JAK family contains four members: JAK1, JAK2, JAK3, and TYK2. STAT family is composed of seven members STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, STAT6, which mainly act as transcription factors.



- **Arsenic trioxide attenuates STAT-3 activity and epithelial-mesenchymal transition through induction of SHP-1 in gastric cancer cells**

Sung Ho Kim †, Hyo Soon Yoo †, Moon Kyung Joo Email author, Taehyun Kim, Jong-Jae Park, Beom Jae Lee, Hoon Jai Chun, Sang Woo Lee and Young-Tae Bak

BMC Cancer 2018 18:150

<https://doi.org/10.1186/s12885-018-4071-9>

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- **ATO effectively inhibits cellular invasion, EMT, and tumorigenesis in gastric cancer cells which are mediated by dephosphorylation of JAK2/STAT3 through increase of SHP-1 expression.**

Anisur Rahman, Khuda-Buksh, Department of Zoology, University of Kalyani, Kalyani, West Bengal, India. Towards understanding molecular mechanisms of action of homeopathic drugs: An overview

#### **National and International Status**

Several research studies undertaken on Arsenicum album in mice models revealed its positive impact in mitigating the arsenic toxicity. This drug also showed growth promoting effect in plant models. However its mechanism of action at cellular level at different potencies used in homeopathy treatments is not well studied.

#### **Materials and Methodology:**

1. **Study setting and design:** Basic biochemical and molecular study.
2. **Study duration:** Twenty four months
3. **Sample size:** Ten to fifteen whole blood samples will be collected from the pathology laboratory of Hamsa Homeopathy Medical College Hospital & Research Centre which will be processed for biochemical investigations.
4. **Sample preparation for Assay:** Determine the protein concentration of each cell lysate and protein to load (Recommended: 10-50 µg/lane) and add an equal volume 2X Laemmli buffer. Reduce and denature the samples by boiling the lysates in sample buffer at 95-100°C for 5 minutes. This step should only be skipped if the antibody datasheet recommends non-reducing or non-denaturing conditions.
5. **Materials required:** Homeopathic preparation of Arsenic album with various potencies will be used in the study. Antibodies required to study the Jak-Stat Pathway will be procured.
6. **Biophysical methods:** Analysis of Arsenic presence in homeopathic drug potencies by bio-physical methods. These are techniques to study the structure, properties, dynamics or function of biomolecules at an atomic or molecular level. They encompass a range of techniques including microscopy, spectroscopy, electrophysiology, single-molecule methods and molecular modelling.
7. **Western Blot technique /Immunoblotting assay:** Western Blotting refers to the electrophoretic transfer of proteins from sodium dodecyl sulfate polyacrylamide gels to sheets of PVDF or nitrocellulose membrane, followed by immunodetection of

proteins using antibodies with fluorescent or chemiluminescent detection. This technique uses antibodies to identify individual proteins within a cell or tissue lysate. Antibodies bind to highly specific sequences of amino acids, known as epitopes. Because amino acid sequences vary from protein to protein, western blotting analysis can be used to identify and quantify a single protein in a lysate that contains thousands of different proteins. First, proteins are separated from each other based on their size by SDS-PAGE gel electrophoresis. Next, the proteins are transferred from the gel to a membrane by application of an electrical current. The membrane can then be processed with primary antibodies specific for target proteins of interest. Next, secondary antibodies bound to enzymes are applied and finally a substrate that reacts with the secondary antibody-bound enzyme is added for detection of the antibody/protein complex.

8. **MTT Assay:** Assay which allow for the quantitative measurement of cell death during cell culture are crucial to any experiment involving ex vivo cellular clinical samples. This colorimetric assay uses reduction of a yellow tetrazolium salt (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, or MTT) to measure cellular metabolic activity as a proxy for cell viability. Viable cells contain NAD(P)H-dependent oxidoreductase enzymes which reduce the MTT reagent to formazan, an insoluble crystalline product with a deep purple colour. Formazan crystals are then dissolved using a solubilizing solution and absorbance is measured at 500-600 nanometres using a plate-reader. The darker the solution, the greater the number of viable and metabolically active cells.

#### **Anticipated Outcome:**

This study confirms the toxic effects of the Arsenic by the homoeopathic drug, namely Arsenicum album, thereby verifying the Law of Similars. The results may show that the potencies which are diluted beyond Avogadro's constant, namely the 30CH and 200CH, have physiological effects on cells, despite having no particles of the original substance present; and verify the theory of hormesis by confirming that different potencies have different effects on cells, with the more dilute potencies having the most stimulatory effects. This study may help comprehensively to prove that succussion does not cause any significant change to the potency when testing on the cellular level. Finally, this study may provide evidence that a biotechnological method could be used to evaluate the physiological effects of homoeopathic potencies on human cells and in this particular study find a solution to cure for "Inflammatory Bowel Disease (IBD)".

#### **Significance of the study and expected benefits**

- **Criticism and scepticism on Homoeopathy not having a scientific basis can be disproved**
- **Mechanism of action of Arsenicum album at cellular level with different potencies used in homeopathy can be studied.**
- **Results obtained would validate the efficacy of homoeopathic drugs**
- **Propaganda of "Homoeopathy – a mere placebo effect" can be eliminated**
- **Effects of ultra dilutions of an otherwise poisonous and oncogenic drug substance can be studied for its therapeutic values in treating Inflammatory Bowel Disease.**

## References

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### **Year-wise Plan of work and targets to be achieved**

#### **Year 1**

- Biophysical estimation of Arsenic in Arsenicum album in Q and other potencies
- Standardization of cell culture conditions and analysis of impact of Arsenicum album with various dilutions on JAK-STAT pathway by western blotting

#### **Year 2**

- Effect of Arsenicum album on cell proliferation and apoptosis would be analysed using MTT assay
- Effect of Arsenicum album would be tested on inflammatory bowel disease at the cellular level by studying the Jak-Stat pathways

### **Details of collaboration, if any intended:**

Collaboration with scientific research experts of Osmania University, a 100-year-old educational and research institution, for cell culture facility and scientist working at Gandhi Medical College are intended

**BUDGET JUSTIFICATION FOR SALARIES, EQUIPMENTS AND BOOKS****SALARY**

S.NO	STAFF	SALARY (As per ICMR)	For 24 Months
1	Research associate (RA)	47000	11,28000
2	SRF	35000	8,40,000
3	JRF	31000	7,44,000
4	Lab assistant	8000	1,92,000
5	<b>Total</b>		<b>29,04,000</b>

**EQUIPMENT**

S.NO	NAME OF THE EQUIPMENT	APPROX. COST
1	UPS with batteries 10kb	4,00,000
2	Laminar air flow	1,50,000
3	Co2 incubator	2,50,000
4	Nitrogen cans	20,000
5	Pipets	20,000
6	Western blot set up	50,000
7	Ultra centrifuge	80,000
8	Microscope	25,000
9	Spectrophotometer	50,000
10	Glass ware	1,0000
11	Electrophoresis	20,000

**BOOKS**

S.NO	TITLE OF THE BOOK	AUTHOR	APPROX. COST
1	Principles and Techniques of Biochemistry and Molecular Biology	Wilson and Walker	3500
2	JAK – STAT Signalling from basics to Disease	Decker & muller	6000
3	Principles of Biochemistry	Lehninger	7000
4	Homoeopathic Pharmacopoeia of India by Dept of AYUSH	Govt of India	1500
5	Material Medica Pura	Hahnemann	3000

**OTHER NON-RECURRING EXPENDITURE**

<b>S.No.</b>	<b>ITEMS</b>	<b>AMOUNT</b>
1	Antibodies & Cell Lines for Cell Culture	2,50,000
2	Computers and Softwares	1,50,000
3	Lab Refrigerator	30,000
4	Consultancy Charges for Computer Lab Set-up	70,000
	<b>Total</b>	<b>5,00,000</b>

**RECURRING EXPENDITURE**

<b>S.No.</b>	<b>ITEMS</b>	<b>AMOUNT</b>
1	Medicines and Chemicals and Glassware	5,00,000
2	Stationery	50,000
3	Printing and Photocopies	20,000
4	Data Entry Charges	1,20,000
5	Computer Utilities	20,000
6	Typing and Printing of Research Reports	10,000
7	Communication Charges	70,000
8	Laboratory Utilities	1,50,000
9	Charges for specialised investigations	1,50,000
10	Electricity	1,10,000
	<b>Total</b>	<b>12,00,000</b>