

*Dedicated*

*To*

*My Beloved Parents*



**Department of Pharmaceutical Engineering and Technology**  
**Indian Institute of Technology**  
**(Banaras Hindu University)**  
**Varanasi – 221 005**

**CERTIFICATE**

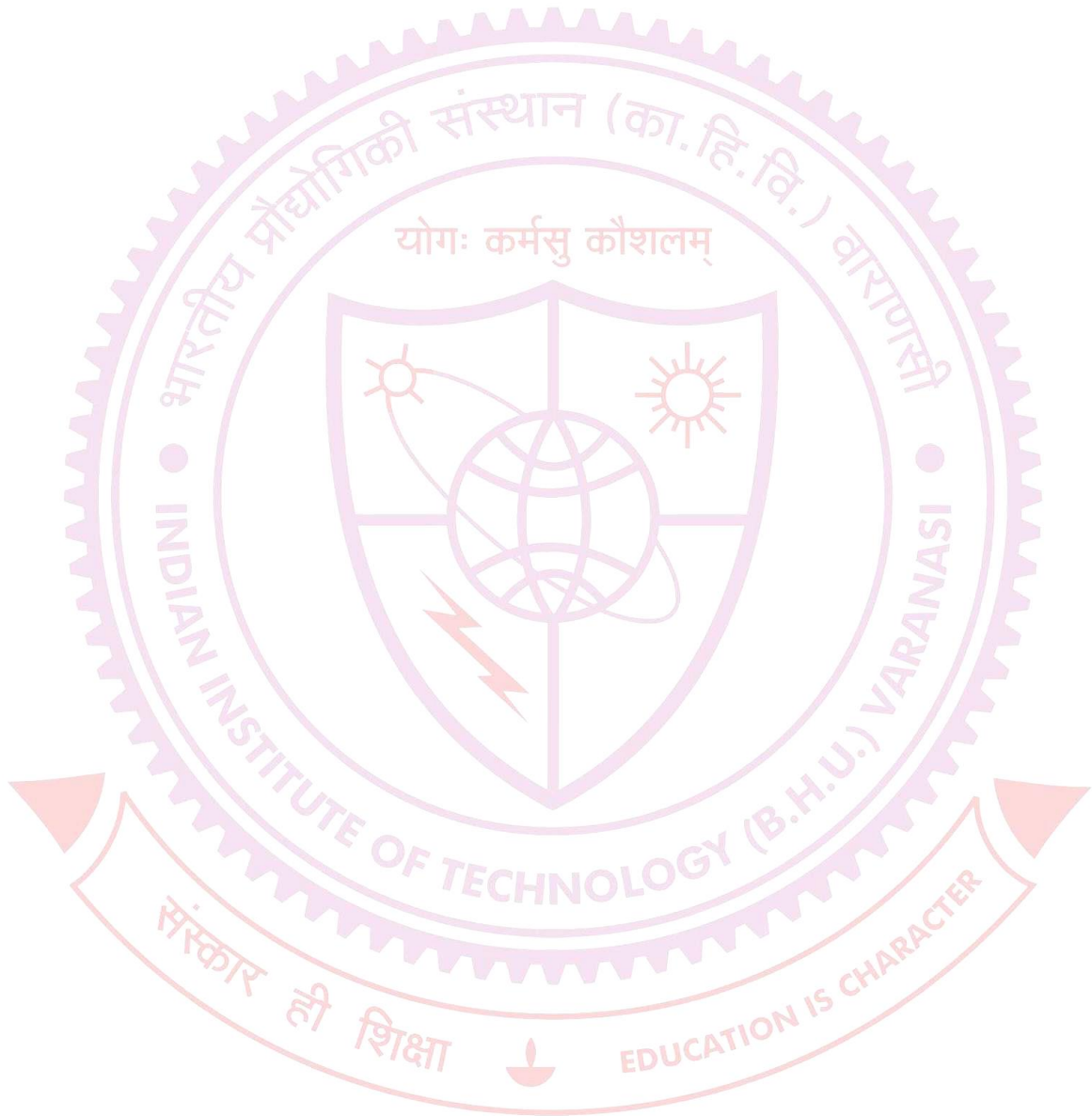
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**Date of Submission:** 17<sup>th</sup> January, 2018

**(Prof. Sushil Kumar Singh)**  
**(Supervisor)**

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It is further certified that the student has fulfilled all the requirements of Comprehensive, Candidacy and SOTA.

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## **DECLARATION BY THE CANDIDATE**

I, AMITABHA DEY, certify that the work embodied in this thesis is my own bonafide work and carried out by me under the supervision of Dr. Vikas Kumar from July, 2013 to August, 2016 at the Department of Pharmaceutics, Indian Institute of Technology (Banaras Hindu University), Varanasi. The matter embodied in this thesis has not been submitted for the award of any other degree/diploma. I declare that I have faithfully acknowledged and given credits to the research workers wherever their works have been cited in my work in this thesis. I further declare that I have not willfully copied any other's work, paragraphs, text, data, results, etc., reported in journals, books, magazines, reports dissertations, theses, etc., or available at websites and have not included them in this thesis and have not cited as my own work.

**Date:** August 19<sup>th</sup>, 2016

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It is certified that the above statement made by the student is correct to the best of my knowledge.

**(Dr. Vikas Kumar)  
Supervisor**

**(Prof. S. K. Singh)  
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**Head of the Department**

संस्कार ही शिक्षा

EDUCATION IS CHARACTER



## **ACKNOWLEDGEMENTS**

---

*At the very outset, I would like to pay tribute to the founder of Banaras Hindu University, **Mahamana Pandit Madan Mohan Malaviya Ji**, who made this glorious holy place of learning.*

*It is definitely a pleasing privilege for me to express my profound sense of gratitude and indebtedness to my venerated teacher and supervisor **Dr. Vikas Kumar**, Associate Professor of Pharmacology, Department of Pharmaceutics, Indian Institute of Technology (Banaras Hindu University), Varanasi, whose profound patience and support were instrumental in accomplishing the project. His scholastic guidance, expert supervision, constant encouragement, steadfast support, affection and inspiration made it possible to conduct the dissertation work smoothly. He has always been a constant source of encouragement and patient bearer of my mistakes. I feel very much honoured and it has been a real privilege for me to get an opportunity to work under him.*

*I am obliged and sincerely thankful to **Prof. Sushil Kumar Singh**, Head, Department of Pharmaceutics, IIT (BHU), Varanasi for providing facilities for my research work. I am obliged to all RPEC and DPGC members for evaluation of my research works.*

*I shall remain thankful to all respected faculty members **Prof. Radhey Shyam Srivastava**, **Prof. Brahmeshwar Mishra**, **Prof. Sanjay Singh**, **Mr. Anand Kumar Srivastava**, **Prof. Sushant Kumar Shrivastava**, **Dr. Sairam Krishnamurthy**, **Dr. (Mrs.) Siva Hemalatha**, **Dr. Senthil Raja Ayyannan**, **Dr. Ashok Kumar**, **Dr. Alakh Niranjana Sahu**, **Dr. Sunil Kumar Mishra**, **Mrs. Ruchi Chawla**, **Dr. Gyan Prakash Modi**, **Dr. Prasanta Kumar Nayak** and **Dr. Madaswamy Sona Muthu** for their co-operation & valuable suggestions during my research work.*

*I am indebted to **Dr. Shyam Sunder Chatterjee**, Retired Head Pharmacologist, Pharmacology Research Laboratories, Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany, for his valuable suggestions & untiring support.*

*I am grateful to Natural Remedies Pvt. Ltd., Bengaluru for providing complementary sample of analytically characterized extracts of *Withania somnifera* along with their HPLC chromatograms.*

*I express my heartfelt gratitude to my senior Dr. Ajit Kumar Thakur for his suggestions, encouragement, keen interest and endless help at every juncture of need.*

*I also express my gratitude to the main library IIT (BHU) and Department library staff for their assistance during the literature review for my dissertation.*

*I feel great pleasure to thank all the supporting staff of the department specially Nandlalji, Md. Rafique Ji, Md. Jameel Ji, Upadhyay Ji, Sanjeev Ji, Yashvant Ji, Sunil Ji and Abhishek for their technical assistance and co-operation throughout my research work.*

*Special thanks to my lab members Mr. Naveen Shivavedi, Mrs. Suruchi Verma and Mr. Mukesh Kumar for their helping-hand and support during my research work.*

*I wish to express a special word of thanks to all research scholars of the Department and junior fellows for their continuous support.*

*The financial assistance in the form of teaching assistant fellowship by Indian Institute of Technology (Banaras Hindu University), Varanasi for this research work is thankfully acknowledged.*

*I am grateful to Indian Institute of Technology (Banaras Hindu University), Varanasi for providing 'Student Travel Grant Support' for presenting my research work in the form of poster presentation at Guwahati, Nagpur and Jordan.*

*Words cannot express my gratitude for my "Maa" and "Baba" for making me capable of reaching this height of education. I owe to the moral support and encouragement they have showered on me and making me what I am.*

*With deepest gratitude and love, I bow down to the Lord Vishwanath for never leaving me alone during the times of trials and suffering and moulding me in what I am today.*

*Last but not least, I am thankful to all persons who directly or indirectly contributed to accomplish this research work.*

*Lastly, I pray to almighty for the 'Moksha' of my experimental animals those little Albino rats and mice, whose sacrifices proved the truth of my thesis work done for the betterment of ailing humanity.*

*Date: August 19<sup>th</sup>, 2016*

*Place: Varanasi*

*(Amitabha Dey)*

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## LIST OF ABBREVIATIONS

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<b>Abbreviations</b>	<b>Full forms</b>
AChE	Acetylcholinesterase
ADP	Adenosine diphosphate
ATP	Adenosine triphosphate
ANOVA	Analysis of variance
AVP	Arginine vasopressin
BChE	Butyrylcholinesterase
CMC	Carboxymethyl cellulose
CAECU	Central Animal Ethical Committee of the University
CNS	Central Nervous System
COX	Cyclooxygenase
CRH	Corticotrophin releasing hormone
DA	Dopamine
IC <sub>50</sub>	Half Maximal Inhibitory Concentration
ELISA	Enzyme Linked Immunosorbant Assay
GABA	Gamma Amino Butyric Acid
GOT	Glutamic oxaloacetic transaminase (Aspartate transaminase)
GPT	Glutamic pyruvic transaminase (Alanine transaminase)
HPA axis	Hypothalamic–Pituitary–Adrenal axis
i.p.	Intraperitoneal injection
MAO	Monoamine oxidase
NAD	Nicotinamide adenine dinucleotide

NMDA	N-methyl-D-aspartate
NSAIDs	Non-Steroidal Anti-inflammatory Drugs
NE	Norepinephrine
NO	Nitric oxide
iNOS	Inducible nitric oxide synthase
NF- $\kappa\beta$	Nuclear factor kappa beta
p.o.	Per oral
SNRIs	Serotonin–Norepinephrine Reuptake Inhibitors
SSRIs	Selective Serotonin Reuptake Inhibitors
5-HT	5-Hydroxytryptamine (Serotonin)
SEM	Standard Error of Mean
TCA	Tricyclic antidepressant
TEG	Triethylene glycol
TNF- $\alpha$	Tumor Necrosis Factor-alpha
WHO	World Health Organization

## LIST OF SYMBOLS

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<b>Symbols</b>	<b>Denotes</b>
$\alpha$	Alpha
$\beta$	Beta
dl	Decilitre
$^{\circ}\text{C}$	Degree Celsius
g	Gram
Hz	Hertz
hr	Hour
kg	Kilogram
IU	International Units
$\mu\text{g}$	Microgram
mA	Milliampere
mg	Milligram
ml	Millilitre
$\mu\text{l}$	Microlitre
min	Minute
ms	Millisecond
ng	Nanogram
%	Percentage
$\pm$	Plus minus
sec	Second
v/v	Volume/volume
w/v	Weight/volume
w/w	Weight/weight
W	Watt
$\times\text{g}$	Times gravity

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## PREFACE

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Ayurveda is the oldest known system of medicine still widely practiced in India and popularity of diverse therapeutic modalities mentioned in ancient Ayurvedic literature has continued to increase during recent decades. In Ayurveda, Rasayana herbs are always recommended for treating metabolic and neurologic conditions. Diabetes is a slowly and silently progressing metabolic disorder, which ultimately leads to structural and functional deteriorations of almost all bodily organs including those of circulating fluids and central and peripheral nervous systems. Diabesity has been associated with various co-morbidities including central nervous system (CNS) disorders such as depression, anxiety, cognitive dysfunctions, and neuropathic pain and inflammation. Treating mental health problems in diabetic patients however remains a challenging field in medical science. Many tonics or rejuvenators oftenly used in Ayurvedic system of medicine for prevention of psychiatric or neurologic comorbidities contain Ashwagandha concoctions as one of their major active ingredients and currently Ashwagandha is recommended by most of Ayurvedic practitioners for treating all such conditions. Ashwagandha (*Withania somnifera*) is a traditionally known rejuvenative herb of solanaceae family, and withanolides are quantitatively the major bioactive secondary metabolites of the plant identified and most currently commercialised *Withania somnifera* extracts or products are now often analytically characterised by their contents of total withanolides. Extensive efforts made during past few decades have identified not only broad spectrums of therapeutically interesting pharmacological properties of diverse types of *Withania somnifera* extracts obtained from different parts, but also of withanolides and other structurally unique bioactive constituents of such extracts. Amongst them the ones dealing with anti-stress, anticancer and anti-inflammatory activities of extracts

rich in withanolides, have attracted the most attention of modern researchers. Preclinical and clinical information now available on diverse types of *Withania somnifera* extracts and numerous of their known bioactive constituents strongly suggest that appropriate combinations of phytochemicals and other bioactive substances encountered in its extracts could as well be used for prevention of metabolic or environmental stress triggered diseases and their syndromes. Keeping in mind, the encouraging withanolides and the data available regarding the use of *Withania somnifera* in treating stress triggered diseases, present study was conducted to fully exploit the potential of *Withania somnifera* in this promising area. The present research work includes the pharmacologically validated rodent bioassays to verify whether parts of the plant other than roots could also be used for the prevention of metabolic or environmental stress triggered diseases and to identify plant metabolites potentially useful for prevention and cure of mental health problems accompanying, or caused by, metabolic diseases. Metabolic effects during stressful conditions using validated behavioural rodent models followed by elucidation of mechanism(s) of observed action(s) through biochemical estimations were evaluated. Observations made during such efforts strongly suggest that, *Withania somnifera* is an adaptogenic Rasayana herb with a uniquely broad psychopharmacological activity profile and could be herbal lead for prevention and treatments of stress triggered diseases commonly associated with metabolic disorders. Further efforts to identify the roles of diverse other known bioactive secondary metabolites of the plant are necessary for better understanding of Ayurvedic pharmacology of this plant.

