Summary

Introduction:
Natural product chemistry has lately undergone explosive growth owing to advances in isolation techniques, synthetic methods, physicochemical measurements, and new concepts. On the other hand, it is precisely the chemistry of natural products, which has fostered many of the new developments in these areas, because of the variety of compound types available. Instances of adverse side effects, or cumulative toxic effects of some chemical compounds of modern medicine, and the escalating cost of modern drugs, resulted in an increased interest in herbal medicines.

Today the global market of herbal products is estimated to be around US $40 billion and growing at a rate of 15-20% annually. The CSIR has been financing several schemes of research on indigenous drugs, CDRI usually gets bulk collections of selected species for phytochemical and pharmacological tests. In continuation of this program on drug discovery and development, phytochemical investigation of medicinal plants and synthesis of different analogues of natural product leads were taken up. The present thesis encompasses the results and discussion of these studies and is divided into four chapters as summarized below:

Chapter 1: Natural Product and Cancer: Review
The review aims to provide comprehensive information regarding different phases related to the history of natural products, chemical constituents isolated from plants and their activity, the chapter also gives introductory information about cancer, types of cancer, plants with anticancer potential, dietary agents of our day to day life with their active constituents responsible for anticancer activity and their molecular targets. The review also covers some popular drugs currently in use to target different types of cancer and the mode of their action.

Chapter 2: Phytochemical investigation of Crataeva nurvala (stem bark)
Crataeva nurvala belongs to Family Capparidaceae, and mainly grows in sub-Himalayan tracts and is indigenous to Tamil Nadu, Kerala and Karnataka. It is found in abundance, in Kerala, Madhya Pradesh, Bengal and Assam. The ethanol extract of stem bark of Crataeva nurvala displayed variety of biological activities therefore, this plant was taken up for detailed chemical and pharmacological investigations, there is enough literature available on the pharmacological and chemical constituent aspect of the plant, our main emphasis was to isolate lead molecule in amount along with other chemical entities, lead molecule (Lupeol) was further derivatized to give, a class of compounds (K1-
K10) called Chalcones, potency of the lead molecule increased on modification when analyzed for Anticancer and Lipid lowering activity. General procedure was followed to obtain lead molecule as well as other constituents.

The dried and powdered plant material (stem bark) was extracted with 95% ethanol by cold percolation method. Solvent was removed under vacuum at 40°C. The ethanolic extract was fractionated into n-hexane, chloroform, Methanol and aqueous fractions. The CHCl₃ fractions of stem bark was considered for detailed chemical investigation. Repeated column chromatography of CHCl₃ fractions afforded five compounds designated as CN-1 to CN-5 from stem bark respectively.

**Compounds isolated from Crataeva nurvala (stem bark)**

The lead molecule (Lupeol, CN-1) afforded Chalcones designated as K1 to K10 through Scheme 1.
**Anticancer activity**:- The Chalcones were tested for breast (MCF-7 and MDA-MB-231) and prostate (PC-3 and DU-145) cancer cell lines, compound K1 (IC\(_{50}\) =18.5µM) and K8 (IC\(_{50}\) = 19 µM) exhibited impressive activity against MCF-7 cell line in comparison to lead molecule (IC\(_{50}\) > 50µM).

![Chemical structures of K1 and K8](image)

**Antidyslipidemic activity**:- The Lupeol derivatives were tested for their lipid lowering potential, compounds K4, K8 and K9 significantly decreased the levels of TC by 24 %, 25%, and 27 %; PL by 25 %, 26% and 25% and TAG by 27 %, 24% and 24% respectively in triton induced hyperlipidemic rats, the molecules exhibited multi prong strategy to achieve it through significant antioxidant activity, increased lipase activity, and reduced HMG-CoA reductase activity.

![Chemical structures of K4, K8 and K9](image)

**Chapter 3: Phytochemical investigation of *Bruguiera cylindrica*(stem bark).**

*Bruguiera cylindrica* belongs to the family Rhizophoraceae and is found in south east Asia with range extending from India and Srilanka through Malaysia, the Philippines, Indonesia and Queensland, Australia.

Large numbers of compounds have been isolated from various species of Bruguiera, containing diverse class of compounds like Alkaloids, Flavonoids, Steroids, Lipids, Carbohydrates, Coumarins,
Sulphur containing compounds, Diterpenes and triterpenes.
The stem bark of the plant was considered for investigation, the CHCl$_3$ fraction of the ethanolic extract was evaluated to obtain chemical entities, four known compounds were isolated from the CHCl$_3$ fraction, which were designated as BC-1 to BC-4, Lupenone (BC-1) was obtained in quantity which was further derivatized to give compounds called Schiff bases for the first time, The Schiff bases (K1–K10) were evaluated for anticancer activity against breast (MCF-7 and MDA-MB-231) and prostrate (PC-3 and DU-145) cancer cell lines while chemical entities isolated from CHCl$_3$ fraction and five Lupenone derived chalcones were tested for Anti- Parkinsonian activity.

Compounds isolated from *Bruguiera cylindrica* (stem bark).

Semi-synthetic scheme undertaken for synthesis of Lupenone derived Schiff bases.

Anticancer activity:- The Schiff bases (K1–K10) were tested for breast (MCF-7 and MDA-MB-231) and prostrate (PC-3 and DU-145) cancer cell lines, compound K1, K5, K7 and K9 were active against both the cell lines of Breast cancer showing activity at a concentration below 50 µM, best activity was displayed by compound K5 (IC$_{50}$ =14.9µM for MCF-7, IC$_{50}$ =18.4µM for MDA-MB-231). The compound was further evaluated for parameters like ROS, mitochondrial membrane potential and western blot in order to determine the apoptotic pathway followed, compound K5
showed significant increase in intracellular ROS at 15µM and 20µM in MCF and at 18 µM and 22µM in MDA-MB-21. K5 brought about appreciable decrease in MMP with increasing concentration in both the cell lines, compound also showed caspase activity but at higher concentration (15,20 µM) in both cell lines, western blot analysis revealed that with increasing concentration of compound, pro-apoptotic proteins like Bax and p53 were upregulated while anti-apoptotic proteins like Bcl-2 were downregulated, the conclusion which can be drawn from the results of above parameters is that apoptosis brought about by K5 is caspase dependent and the cumulative effect ROS, activated caspase, decreased MMP and upregulation of pro-apoptotic proteins resulted in achieving apoptosis.

**Antiparkinsonian activity:** Out of the nine molecules tested for the activity, four were chemical entities isolated from CHCl₃ fraction of the crude extract and five were Lupenone derivatives, all the molecules were analyzed for alpha synuclein aggregation, a parameter for determining Parkinson’s. Lupenone designated as B.C-1 was found to be the most effective molecule along with K002, these two molecules were further examined for parameters like dopamine signaling using nonanol repulsion assay, Reactive Oxygen Species (ROS) and daf-16 nuclear localization, findings exhibited
Summary

that Lupenone brought about significant reduction in aggregation of alpha synuclein protein, increased dopamine signaling, increased localization of DAF-16::GFP in C.elegans and last but not the least, posses free radical scavenging potential. Lupenone with all these properties could serve as antiparkinsonian molecule and modification could enhance its potency.

Chapter 4: Phytochemical investigation of *Xylocarpus granatum* (fruit).

*Xylocarpus granatum* belongs to the family Maliaceae and is found in East Africa, South Asia, Australia and the Pacific Islands. In India it occurs in coastal area of South up to Maharashtra and in Andaman Islands.

Number of compounds have been isolated from three species of Xylocarpus, most of which belong to the class Liminoids. The part of the plant investigated was fruit, the CHCl₃ fraction of the ethanolic extract was chromatographed to obtain four chemical entities, which were designated as XG-1 to XG-4. Photogedunin (XG-2) was evaluated for its anti-adipogenic potential, various parameters were considered for the purpose like Oil Red-O (ORO) staining, Real Time PCR, Cell cycle analysis. Two cell lines (3T3L-1 and C3H10T1/2) were used to assess the anti-adipogenic potential in time dependent (0–2, 0-4, 0-6 days) and concentration dependent (5,10,20μM) manner, results were encouraging which prompted us to go for further analysis , real time PCR reveals molecule at 20μM brings about significant reduction in gene level expression of adipogenesis associated genes viz. PPARγ, C/EBPα and ap-2 in 3T3-L1 cell line and FACS analysis demonstrated that photogedunin arrests the cells in G1/S phase of cell cycle.
Compounds isolated from *Xylocarpus granatum* (fruit).

![Chemical structures of compounds from *Xylocarpus granatum*](image)

Our work embodies the effects of natural and semi synthetic entities on cancer, dyslipidemia and neurodegenerative diseases, the rationale behind investigating these specific diseases lies in the fact that all three are either correlated / have common pathways, relation between all the three disease can be established by emphasizing on PI3K-AKT pathway which is involved in wide variety other metabolic actions. AKT pathway gets up-regulated in cancer and is considered major reason for malignancy, AKT/mTOR activation is necessary for adipogenesis/ lipogenesis programming and the pathway gets modulated by DJ-1 and PARKIN in PD, work of Casey et.al and review by Kitagishi et.al gives insight into the relation. The studies have yielded us molecules which are potent against all the three diseases separately but a common molecule which could be effective against all the three diseases remains an illusion. The leads from the above work could pave the way for better development of potent drugs. To say the least, natural products have proved to be the backbone of drug industry as most of synthetic drugs available today are either inspired from natural compounds or mimic their structure or activity.