Development of Novel Phospholipase A2 Inhibitors Using Molecular and Computational Techniques

Manoj G Tyagi*, Dinesh J Vyas, Vinita Ernest And Debjyoti Mukherjee

Department Of Pharmaceutical Chemistry, VIT, Vellore & Department Of Pharmacy, Monash University School Of Medicine, Selangor, Malaysia*

Corresponding Author: Manoj G Tyagi

Abstract: Phospholipase A2 Enzymes Are Basically Of Three Types. I.e. The Cytosolic PLA2, Secretory PLA2 And Lipoprotein Associated PLA2. There Is Growing Interest In Developing Novel And Potent PLA2 Inhibitors For Various Therapeutic Purposes. E.g. Alzheimer’s Disease, Allergic Conditions, Arthritis And Cancer, Cardiovascular Disorders And To Counter The Envenomation By Bee, Spider And Snake Bites. One Of The Excellent Example Is Darapladib Which Is An Effective And Potent Inhibitor Of The Lipoprotein Associated PLA2. And Is Used For Clinical Conditions. On The Other Hand, Computational Studies Conducted On The Numerous Snake Species Having Endogenous Phospholipase A2 Inhibitors, Can Be Exploited For Therapeutic Purposes. This Inhibitor Type Is Generally Known As Snake Blood Phospholipase A2 Inhibitors (Sbplis). Most, If Not All Sbplis Are Oligomeric Glycosylated Proteins, Although The Carbohydrate Moiety May Not Be Important For PLA2 Inhibition In Most Cases. Western Blot Analysis After Partial Purification With SPLA2-IB Affinity Column Has Confirmed The Identity Of Serum Spla2 Binding Protein As A Soluble Form Of PLA2R (SPLA2f) That Retained All Of The Extracellular Domains Of The Membrane-Bound Receptor. This Review Article Has Tried To Encompass The Recent Advances In The Development Of Novel And Potent PLA2 Inhibitors, Both Endogenous And Synthetic In Nature.

Key Words: Phospholipase A2, Inhibitors, Endogenous, Crotoxin, Lipoprotein, Molecular, Therapeutic

Date of Submission: 05-03-2018

Date of acceptance: 23-03-2018

I. Introduction:

Phospholipase A2 Enzymes Are Basically Of Three Types. I.e. The Cytosolic PLA2, Secretory PLA2 And Lipoprotein Associated PLA2. Phospholipase A2 (PLA2) Is An Enzyme That Catalyzes The Hydrolysis Of The Sn-2 Ester Bond Of Glycerophospholipids Thereby Causing The Release Of The Arachidonic Acid (1, 2). Since Its Discovery, PLA2 Has Been A Molecular Target Of Extensive Research Because Of Its Critical Involvement In Physiological And Pathological Events Such As Phospholipid Turnover And Production Of Pro-Inflammatory Lipid Mediators (3). To Date, A Number Of Mammalian Intracellular And Extracellular PLA2s Have Been Identified And Classified Into Different Families According To Their Biochemical Features (4). Amongst Them, Spla2s Have Several Common Characteristics Including A Relatively Low Molecular Mass (14-18 Kda), The Presence Of 6 To 8 Disulfide Bridges, And An Absolute Catalytic Requirement For Millimolar Concentrations Of Ca2+ (5, 6). Recent Studies Show The Evidence For The Existence Of Circulating Phospholipase A2 Inhibitors Against Secretory PLA2s (Spla2s) In Mammals. In Mouse Serum, Detection Of Specific Binding Activities Of Group IB And X Spla2s (Spla2-IB And Spla2-X), Which Was In Contrast With The Absence Of Binding Activities In Serum Prepared From Mice Deficient In PLA2 Receptor (PLA2R), A Type I Transmembrane Glycoprotein Related To The C-Type Animal Lectin Family. Western Blot Analysis After Partial Purification With Spla2-IB Affinity Column Confirmed The Identity Of Serum Spla2 Binding Protein As A Soluble Form Of PLA2R (Spla2f) That Retained All Of The Extracellular Domains Of The Membrane-Bound Receptor (7-8). In A Recently Published Article This Author Has Nicely Depicted The Importance Of The Lipoprotein Associated PLA2. Also Known As The PAF Acetylhydrolase (9). There Is Growing Interest In The Development Of Both Endogenously Found And Synthetic PLA2 Inhibitors And For This Purpose Molecular And Computational Methods Are Being Exploited. This Review Article Tries To Evaluate The Recent Progress In The Development Of Novel PLA2 Inhibitors For The Purpose Of Therapeutic Usage.

CNF And Related Peptides Used For Countering The PLA2: The Endogenously Found crotalus Neutralizing Factor (CNF) – Encodes A 19-Residue Signal Peptide Characteristic Of Secreted Proteins, Followed By 181 Amino Acids In The Mature Protein, Including Sixteen Cysteines. CNF Is A Glycosylated Alphal-Globulin With A Single N-Terminal Linked Carbohydrate Site At Asn157 (10-11). The Carbohydrate Moiety, However, Is

DOI: 10.9790/3008-1302020512

www.iosrjournals.org

5 | Page
Not Essential For PLA₂ Inhibition, Since CNF Remains Functional After Enzymatic Deglycosylation (12). The Native CNF Is A Globular-Shaped, Predominantly Tetrameric Molecule With An Average Molecular Mass Of 100 Kda In Solution. It Innately Occurs As A Mixture Of Non-Glycosylated And Glycosylated Monomers Of 22 Kda And 25 Kda, Respectively (13). The Oligomerization Of CNF Is Independent Of The Presence Of Carbohydrates, Since It Occurs Equally With Native Or Enzymatically Deglycosylated Monomers. Tyrosine Residues At The Interface Of The Monomers Composing CNF May Contribute To The Oligomerization Process, According To A Proposed Theoretical Structural Model Constructed For The Inhibitor Available With DOI:10.5452/Ma-Av444 At Modelarchive Database. The U Monomer Of The Crystallographic Structure Of Urokinase Plasminogen Activator From Homo Sapiens (PDB ID: 2FD6) Was Used As The Template Ab Initio (14). Besides Inhibiting Lethal And PLA₂ Actions Of C. D. Terrificus Venom, CNF Is Also Able To Inhibit The Lethal Activity Of Heterologous Viperid Venoms, Such As Those From Bothropsalternatus, B. Atrox, B. Jararaca. B. Jararacussu, B. Mookjy, B. Neuwiedi And Lachesis Muta, But Not That Of The Elapid Micrurus Frontalis (15). The Natural Target Of CNF In Homologous Venom Is Crotoxin, A Heterodimeric B-Neurotoxin Formed By An Enzymatically Inactive Subunit (Crotoxin A Or CA) And A PLA₂ Counterpart (Crotoxin B Or CB). CA And CB Are Non-Covalently Bonded In The Crotoxin Complex (CA/CB). CNF Is Able To Displace CA In The Native Crotoxin In Vitro To Form A Non-Toxic CNF/CB Complex, Most Likely At A 1:1 Molar Ratio (16). In The Presence Of CNF, The Newly Formed CNF/CB Complex No Longer Interacts With The Target Acceptor Of Crotoxin On Rat Synaptosomes To Deliver CB To Cause Its Neurotoxic Effect.

Lp-PLA₂ Inhibitors:PAF Acetylhydrolase Or LP-PLA₂ Is An Important Enzyme Under Intensive Scrutiny. An Alternative Permeability-Inducing Agent In Diabetic Retina Could Be Lysophosphatidylcholine (LPC), Which Is Increased In Plasma Of Diabetic Patients (17) And Has Demonstrated Permeability Enhancing Activity In Cultured Non-Neural Endothelial Cells (Ecs). The Principal Enzyme Responsible For The Production Of LPC Is A Calcium-Independent Phospholipase A₂, Called Lipoprotein-Associated Phospholipase A₂ (Lp-PLA₂) Which Is Also Known Astype VIIA PLA₂ (18). Darapladib, A Specific Inhibitor Of Lp-PLA₂, Has Been Shown To Reduce Atherosclerosis In Both Diabetic/Hypercholesterolemic Pigs (19-20) And Apor-Deficient Mice (21). In Diabetic/Hypercholesterolemic Pigs, Darapladib Protected Against Blood–Brain Barrier (BBB) Dysfunction And Vascular Permeability. Darapladib Has Been Studied In Nearly 16,000 Patients With Coronary Heart Disease, And Approximately One-third Of This Study Population Had Diabetes Mellitus (22). In A Further Study, A 3-Month Daily Treatment With 160 Mg Of Darapladib Orally Showed Reduction Of DME, And An Improvement In Visual Acuity In Patients (23). Another Lp-PLA₂ Inhibitor And Congener Developed By Glaxo Smith Kline i.e GSK2647544 Is A Potent And Specific Inhibitor Of Lipoprotein-Associated Phospholipase A₂ (Lp-PLA₂), Which Was In Development As A Potential Treatment For Alzheimer’s Disease (AD). In Order To Refine Therapeutic Dose Predictions And Confirm Brain Penetration, A Radiolabelled Form Of The Inhibitor, [¹⁸⁸F]GSK2647544, Was Developed For Use In A Positron Emission Tomography (PET) Biodistribution Study, The Study Provides Evidence That GSK2647544 Is Able To Cross The Blood Brain Barrier In Healthy Male Subjects Leading To A Measurable Brain Exposure. The Administered Doses Of GSK2647544 Were Well Tolerated. Exploratory Modelling Studies Suggested That A Twice-Daily Dose Of 102 mg, At Steady State, Would Induce ~80 % Trough Inhibition Of Brain Lp-PLA₂ Activity. Thus New Congeners Which Effectively Inhibit The Lp-PLA₂ Are Being Investigated.

Computational Studies On Novel PLA₂ Inhibitors:There Are Many Reports Where Computational Molecular Modeling Methods Have Been Used For Characterizing Some Functional Aspects Of PLA₂, Or The Development Of PLA₂ Inhibitors That Contribute To The Attenuation Or Annihilation Of Snake Venom Toxicity. These Applications Use The X-Ray Crystallographic 3D Structural Information Generated In The Last Few Decades, And Methods Such As Molecular Dynamics (MD) Simulations And Docking. Structural Architecture Of Snake Venom PLA₂s Is Divided Into Classes I And II, Based On Their Amino Acid Sequence And Disulfide Bonding Pattern (24). However, They Have A Conserved Structure Which Contains An N-Terminal A-Helix (H1), A Ca²⁺Binding Loop, Two Antiparallel A-Helices (H2 And H3), A Two-Stranded Antiparallel Sheet (B-Wing), And A Long C-Terminal Loop. In General, Folding Is Stabilized By Seven Disulfide Bonds With Different Types Of Pattern In Classes I And II. Some PLA₂s Undergoaggregation In A Concentration-Dependent Manner. Crystal Structures Available For Several PLA₂s Confirm That They Can Form Associations In Dimer, And More Units With Physiological Implications. The Majority Of Molecular Modeling Applications In Literature For Studying PLA₂s Are Oriented To Rational Design Of Novel Inhibitors For The Treatment Of Different Viperidaevenom. Some Examples Are Cited Here Which Are Described: Most Examples Have Been Applied To PLA₂ Of DaboiaRusselli. Recently, Nagrot et al (25) Evaluated A Library Of Natural Products And Synthetic Molecules Through Docking Studies On D. Russelli/PLA₂ To Identify Possible Inhibitors. Their Study Lead To In Silico Identification Of Several Molecules As PLA₂ Inhibitors, With Most Of Them Belonging To Phenolic And Substituted Benzaldehydiccompounds. It Is Important To Note That The Selection In This Work Was Performed By Considering Docking Energy Scores,
Which Is A Reliable Criterion, According To Literature. The Same Authors Proposed The Docking Poses Inside PLα1 Of D. Russelitorf Synthetic Phenolic Compounds Effective Against Snake Venom. They Found That Phenolic Compounds Having Hydroxyl And Methoxy Groups In Their Benzene Ring Showed Maximum Inhibitory Potency. The Majority Of Molecular Modeling Applications In Literature For Studying PLα2s Are Oriented To Rational Design Of Novel Inhibitors For The Treatment Of Different Viperidae snakebites. Snake Bite Is A Serious Global Problem, Especially In Countries With Subtropical Climate Like India, Phillipines And Other South East Asian Countries. Phenolipases A2 (PLα2s) Commonly Found In Snake Venom, Are Extensively Studied Due To Their Pharmacological And Physio-Pathological Effects. Numerous Plant Species Are Used In Folk Medicine To Treat Venomous Snake Bite Without Scientific Validation. A Good Example Is The Indian Medicinal Ricenjavavarwhich Is A Unique Medicinal Variety Rice In Kerala Used In Ayurveda For Many Disease Conditions Including Snake Bite Pustules. In This Published Report, Bioactive Compounds Isolated From Njavarawere Screened As Inhibitors, Against The Indian Russell ‘S Viper PLα2 (PDB Id: 1TH6) Using Molecular Docking Techniques (26). Phytochemical Investigation Of Njavara Led To Isolation Of Six Compounds For The First Time Including Bioactive Phenolic Acids (Ferulic, Syringic, Vanillic And Protocatechuic Acid), B-Sitosterol, And 2-Methylene Cycloartanylferrulate.

On The Other Hand Another Form Of PLα2, Group VIA Calcium-Independent (GVIA Ipla2), And Group V Secreted (GV SPLα2) Enzymes Are Implicated In Many Inflammatory Diseases (27). Thus, The Development Of Potent And Selective Inhibitors For Each Of These Three Enzymes Should Lead To The Development Of Novel Pharmaceutical Agents For Different Inflammatory Conditions. GIVA CPLα2 Was Cloned And Sequenced In 1991and Its Crystal Structure Was Reported In The Year 1999. This Enzyme Utilizes A Catalytic Dyad Of Ser/Asp, And It Exhibits High Specificity For Membrane Phospholipids Containing Arachidonic Acid (AA) At The Sn-2 Position. Thus, It Is The Main AA Provider For The Cylooxygenase (COX) And 5-Lipooxygenase (LOX) Pathways. Therefore, This Enzyme Can Be Considered A Key Enzyme For Mediating Production Of Eicosanoids Which Are Implicated In Numerous Inflammatory Diseases (28).

A Variety Of Diverse Small Molecule Inhibitors Against PLα2 Have Also Been Reported And Their Structures Are Summarized In Some Review Articles. These Groups Have Developed Some Novel Classes Of Inhibitors Including 2-Oxoamides For GIVA Cpla2amides For GV sPLα2, And Fluoroketones For GVIA Ipla2. They Have Now Explored Potent And Selective Inhibitors For GVIA Ipla2 Using Structure-Based Design And In Vitro Mixed Micelle Assays. Even Though There Is No Available Crystal Structure For This Enzyme, A Robust Homology Model Was Developed Based On Hydrogen/Deuterium Exchange Mass Spectrometry (DXMS) Experimental Data And Molecular Dynamics (MD) Simulations. The 3D Structure Of GVIA Ipla2 Was Used For Molecular Docking Calculations And MD Simulations With Previously Synthesized Inhibitors In An Effort To Establish A Structure-Activity Relationship (SAR) For The Development Of Novel And Potent Inhibitors.

Common Techniques Employed In Developing A Novel PLα2 inhibitor:

Molecular Docking

Molecular Docking Can Be Done Using Several Techniques And Softwares For e.g., The Virtual Screening And Docking Can Be Performed Using Autodockvina. Autodockvinas Used Due To Its Accuracy And Speed. Autodockvinais Utilized To Automate The Docking Process Towards The NADI Compounds. The Predicted Binding Energy (ΔG), Which Indicates The Strength Of Compounds Bind To The Receptor Is Calculated Based On Scoring Function Used In Autodockvina. The Top Ten Docking Conformations For Each Compound Is Selected Using A Python Script File. The Selection Is Based On Lowest Energy Binding. The H-Bond, And Hydrophobic Interaction Areanalysed Using Ligplotserver (29-30) And Viewed Using A Discovery Studio Visualizer (Refer Fig.2).

Inhibition Of PLα2 Activity

The Inhibitory Activity Of PLα2 Can Be Tested According To The Method Described By De Aranjo And Radvany (31). Briefly, The Substrate Consisted Of 3.5 Mm Lecithin, A Mixture Of 3 Mm NATDC, 100 Mm NACl, 10 Mm CaCl2, And 0.055 Mm Red Phenol As Colorimetric Indicator. And 100 Ml H2O. The pH Of The Reaction Mixture Was Adjusted To 7.6. 0.2 Mg Of Pg-IB Is Solubilized In 10% Acetonitrile At A 0.002 Mg/Ml Concentration. A Volume Of 2 Ml Of PLα2 Solution Is Incubated With 2 Ml Of Sample For 20 Min At Room Temperature. Then, 200 Ml Of PLα2 Substrate Was Added To The Solution. Kinetic Hydrolysis Is Performed For 5 Min, And Optical Density Is Estimated At 558 Nm. The PLα2 Inhibitory Activity Is Expressed In Inhibition Percentage And Is Calculated As Follows:

\[
\text{Enzyme Activity=ODzero−OD15 Min/15 Min% Inhibition=Enzyme Activity−Ve Control− Enzyme Activity sample/enzyme Activity−ve Control × 100}
\]
Immunoblotting Analyses: Immunoblotting Or Western Blotting Is An Effective Technique To Identify Novel Proteins And Their Molecular Mass. For Western Blotting Analyses, Proteins Are Transferred To A Nylon Membrane, Which Is Subsequently Blocked (1 H, Room Temperature) With Tris-Buffered Saline-Tween (TBS-T, Which Contains 20 Mm Tris-HCl, 137 Mm NaCl, Ph 7.6, And 0.1% Tween 20) Containing 1% BSA And 3% Milk Powder (32). Following Three Washes With TBS-T, The Blot Was Then Incubated (1 H, Room Temperature) With A Monoclonal Antibody (1:50 Dilution In TBS-T With 1% BSA) Raised In A Mouse Against A Synthetic Peptide Representing A 10-Amino Acid Residue Sequence (221TPLHLACQMG230) Located At The C Terminus Of Islet Cai-PLA2. The Nylon Membrane Is Washed Three Times In TBS-T And Incubated (1 H, Room Temperature) With A Goat Anti-Mouse IgG Conjugated To Horseradish Peroxidase (Boehringer Mannheim) At A 1:3000 Dilution In TBS-T Containing 1% BSA. Detection Of The Secondary Antibody Is Performed By Enhanced Chemiluminescence (Refer Fig.1).

Monoclonal Antibody Against Snake PLA2: Monoclonal Antibodies Are Increasingly Being Used For Therapeutic Purpose In Disorders Like The Bronchial Asthma, Arthritis, Psoriasis And Cancer. The Snake Venom PLA2s (SvPLA2) Are Important Toxins And Comprise An Important Target For The Development Of New Anti-Venom Drugs. Snake And/Or Mammals Serum Are Repositories Of Svpla2 Inhibitors (PLis) Due To Protective Benefits (33). Immunodetection Is An Essential Technique Commonly Employed For Protein Discovery, Quantification And Investigation. Thus, Mab Development Of Plıγ Is Technically Significant For Anti-Venom Studies. The Classical Routine Of Monoclonal Antibody Preparation Is Time Consuming And Laborious; The Resulted Mabs Are Generally Very Specific. Protein-Specific Antibodies Can Be Generated By Immunization Of Animals With Peptides. If The Peptide Is An Effective Epitope Of The Protein, Bioinformatics Prediction Followed By Concrete Experimental Validation Is Both Economical And Effective. For Epitope Prediction, Bioinformatics Software Can Reduce The Experimental Workload By 95% And Increase The Efficiency Of New Epitope Location By 10 To 20 Folds. In This Study, Dnastar Protean Program Was Used To Predict Epitopes Of Saplıγ By Comprehensively Analyzing Many Parameters Such As Hydrophilicity, Surface Accessibility, Antigenic Index, Secondary Structure And Flexibility. Finally, The 151CPVLRLSRHEANRNDK172 As A Hapten And Obtained 18 IgG Mab Cell Strains. The Resulted Plymab Could Recognize A Broad Range Of Snake Sera Including Venomous And Non-Venomous Snake Species, Because The Epitope Peptide Is Highly Homologous Among Snake Pliγs. The Resulted Mab Is Applicable For Plyimmunodetection Of A Wide Range Of Snake Species (34).

Natural And Synthetic Inhibitors Of PLA2:
Manoalide Was Initially Isolated From The Sponge Luffatiellavariabilis. Because Of Its Potent Anti-Inflammatory And Analgesic Effects, This Compound Is Now In Phase 1 Clinical Trial. Although This Agent Is Not Clinically Available, Manoalide Becomes A Standard Drug In Inflammation Research (35-36). The Other PLA2 Inhibitors Are Variabilin, Cacospongiolide B, Bolinaquinone, And OAS1000 (35). Bromelain And Phytochemicals Like Amenthoflavone, Asiaticoside, And Diosgenin Have Been Reported To Exhibit Inhibitory Effects Against PLA2 Activity (37-38). Bromelain, Asiaticoside And Diosgenin Appear To Be Safe Compounds, As They Do Not Show Any Toxic Effects With A Lethal Dose (LD50) Of Up To 750 Mg/Kg In Dogs, 50 Mg/Kg In Mice And More Than 800 Mg/Kg In Mice, Respectively. It Was Also Discovered That The Combination Of Phytochemical Compounds With Bromelain Could Enhance The Functional Properties And Thermal Stability And Increase The Shelf Life Of Pineapple Juice. The Combinations With Natural Products, Including Bromelain, Was Also Proven To Enhance The Effect Of Other Anti-Inflammatory Drugs Such As Paracetamol In The Relief Of The Knee Joint Pain (39). The Effect Of The Combination Between Bromelain And Antibiotics Was Shown To Be More Effective Compared To Antibiotics Alone In The Treatment Of Pneumonia, Bronchitis And Cellulitis (40-42).

In This Study, The Synergistic Potential Of Combinations Of Bromelain And Phytochemicals Namely, Amenthoflavone, Asiaticoside, And Diosgenin, Against PLA2 Was Quantified. The Combinations Of Bromelain-Amenthoflavone (Br-Am), Bromelain-Asiaticoside (Br-As), And Bromelain-Diosgenin (Br-Di) Were Analyzed Using A Protocol Which Is Widely Used To Determine The Synergistic And Antagonistic Effects In Combination Studies. Subsequently, Proof Of The Utility Of The Bromelain-Phytochemical Complex Were Generated By Measuring The Inhibitory Activity Against PLA2 (43). Flavonoids Too Have Been Investigated For PLA2 Inhibitory Activity. The Inhibition Of PLA2 by Polyphenolic Flavonoids Has Been Reported In A Number Of In Vitro And In Vivo Studies. Quercetin Was Found To Be An Effective Inhibitor Of PLA2 In Human Leukocytes. Bioflavonoids Such As Amenthoflavone, Bilobetin, Morelloflavone And Gingkotin Derived From Certain Medicinal Plants Have Been Shown To Inhibit PLA2 As Well. Curcumin Affects Arachidonic Acid Metabolism By Blocking The Phosphorylation Of Cytosolic PLA2, Resulting In Decreased COX-2 Expression. Since PLA2 Is Coupled With Coxs And Loxs Depending On The Cells, PLA2 Becomes The Molecular Target Of Polyphenols To Cause The Inhibition Of COX Or LOX Activity And Inflammation (44).

DOI: 10.9790/3008-1302020512 www.iorsjournals.org 8 | Page
II. Conclusion:

Phospholipase A2 (PLA2) Enzymes Are A Diverse Group That Hydrolyze Membrane Phospholipids Into Arachidonic Acid And Lysophospholipids. These Lipid Mediators Play Critical Roles In The Induction, Maintenance, And Modulation Of Neuroinflammation And Oxidative Stress. Many Neurological Disorders Including Excitotoxicity; Traumatic Nerve And Brain Injury; Cerebral Ischemia; Alzheimer’s Disease; Parkinson’s Disease; Multiple Sclerosis; Experimental Allergic Encephalitis; Pain; Depression; Bipolar Disorder; Schizophrenia And Also Cardiovascular Disorders Are Characterized By Oxidative Stress,
Inflammatory Reactions And Alterations In Phospholipid Metabolism, Accumulation Of Lipid Peroxides, And Increased Activities Of Brain Phospholipase A₁ Isoforms. Many Old And New Synthetic Inhibitors Of PLA₂, Including Fatty Acid Trifluoroalkyl Ketones; Methyl Arachidonylfluorophosphate; Bromoenoil Lactone; Indole-Based Inhibitors; Pyrrolidine-Based Inhibitors; Amidine Inhibitors, 2-Oxooamides; 1,3-Disubstituted Propan-2-Ones And Polylfluoroalkyl Ketones As Well As Phytochemical Based Inhibitors Including Curcumin, Ginkgo Biloba And Centellaasiatica Extracts Have Been Discovered And Used For The Treatment Of Classical Diarrhea In Cell Culture And Animal Model Systems. The Blood Of Poisonous Snakes Contain PLA₂ Inhibitors Whose Structure Activity Relationship Can Be Used For Developing Potent PLA₂ Inhibitors For Treating Envenomation And Other Pathological Disorders. The Purpose Of This Review Was To Summarize Information On Selective And Potent Synthetic Inhibitors Of PLA₂ As Well As Several PLA₂ Inhibitors From Plants And Endogenous PLA₂ Inhibitors From Marine And Snake Species For Therapeutic Purposes.

Acknowledgements: The Authors Thank Ms. Vishakha Tyagi, MSc., For Her Help Towards This Research Article.

References:
Development Of Novel Phospholipasea2 Inhibitors Using Molecular And Computational Techniques


[33] Jingjing, Yingxiang, Shirmin Sun, Lehan Yu, And Chunhong Huang Preparation Of Monoclonal Antibodies Against Gamma-Type Phospholipase A2; Inhibitors And Immunodetection Of These Proteins In Snake Blood Venom Anim.Toxinsinul Trop Dis. 2017; 23: 37.


[43] Fatahiya Mohamed Tap,Fadzlilahdibhabab Majid,Hassan Falmi Ismail,Tet Soon Wong,Kamyarshameli,MKio Miyake And Nurulbahiyah Ahmad Kharidn In Silico And In Vitro Study Of The Bromelain-Phytochemical Complex Inhibition Of Phospholipase A2 (Pla2), Molecules 2018, 23(1), 73.