Contemporary investigations on design of ER modulators across the globe are being directed towards the development of newer agents for HRT, targeting malignancies of the female reproductive system, for contraception as well as for infertility and other estrogen related pathological conditions. The associated risk factors of the available current therapies will quite possibly be reduced at dramatic rate owing to rational modeling and design of highly target sensitive molecules. The significant outcome of in-silico applications in elucidating ER binding properties of chemical compounds have demonstrated prospective usefulness of such technique in drug development. This is more so, as CADD can provide valuable information for small-molecular screening and optimization.

Keeping in harmony with present-day research trends, major portion of the work undertaken could highlight on approaches of cheminformatics application in elucidating the fundamental biophore arrangements as applied to different non-steroidal estrogenic compounds. During the study, different approaches like 2D and 3D QSAR, structural similarity and pharmacophore space modeling methodologies have been applied for biophore finger-printing and subsequent model development for predicting better active molecules. Ten diverse congeneric series have been screened in the process, from which different possibilities regarding biophore arrangements for these series of compounds and suggestive models for design of better active compounds could be discussed, based on statistical significance and predictive coefficients of models developed. The primary outcomes of the investigation revealed several universal features for estrogenic activity. Firstly, attachment of aryl ring systems to unsaturated linkages within a molecular framework might be grossly important for estrogenic activity, as this feature has been observed to be essential while modeling of 4 different classes, viz. trifluoromethyl triphenylethlenes, bromotriphenylethlenes, flavonoids and bridged-cyclic diarylhydroxyls. The attachments of cyclic ring systems to unsaturated bond possibly provide extra conformational rigidity of the compounds for binding at ER surfaces. Secondly, presence of both nucleophilic as well as electrophilic attachments in ring systems within close proximity can also be crucial in flavonoids, tetrahydroisoquinolines, arylocyclohexanecarboxylic acids, bridged-cyclic diarylhydroxyls, bridged - oxabicyclic diarylethylenes and raloxifene derivatives. Arrangement of different type of substituents in close proximity suggests involvement of dissimilar binding regions in close association at the receptor surface. However, existence of only one of the features is also found to be important in trifluoromethyl triphenylethlenes and alkylphenols (for electron donating groups only), and bromotriphenylethlenes and triphenylacrylonitriles (for electron withdrawing groups only). The importance of phenolic hydroxyl group for estrogenic activity is also figured out to be vital in triphenylacrylonitriles, bridged-cyclic diarylhydroxyls and raloxifene derivatives. In addition to these properties, global hydrophobicity or hydrophobic regions within molecular species has also been witnessed to be crucial in bromotriphenylethlenes, tetrahydroisoquinolines, bridged-oxabicyclic diarylethylenes and raloxifene derivatives. Thus it may be further concluded that there is also involvement of hydrophobic regions within receptor site and incorporation of hydrophobic fragments to these
group of molecules might further aid to design of better active molecules. Finally, the configuration of certain functional group attachments to the molecules has been deduced to be important in cases of bromotriphenylethlenes, arylelcyclohexanecarboxylic acids, bridged-oxabicyclic diarylethlenes and raloxifene derivatives. Therefore, stereochemistry of the functional groups attached to non-steroidal estrogens might further affect the bioactivity. Apart from these, supplementary features like branching\textsuperscript{323}, orientation along with conformational rigidity, ionization potential and molecular size\textsuperscript{153} have additionally been discussed to be vital in a certain number of cases. With regards to pharmacophore space modeling, HB acceptor-lipid, HB donor, hydrophobic and ring aromatic features are explored to be important for breast cancer cell-line inhibition of raloxifene derivatives; while HB acceptor, hydrophobic and ring aromatic features are figured to be important for ER binding affinities of bridged-cyclic diaryl compounds. Even though most of the models reflect good statistical significance and predictive ability, still more data points with wider coverage of structural features need to be taken into account to get better insight into structure-activity relationships.

The recent upsurge in exploitation of natural resources for possible medicinal values with reduced toxicity has triggered research efforts in this area on a more rational basis. It is known that steroidal contraceptives bear number of side effects affecting the human cardio-vascular system in particular, causing alteration in lipid and carbohydrate profiles\textsuperscript{185,191}. As such present day investigations focus on minimizing this factor yet retaining optimum contraceptive activity. The present work on investigation of tape-vine leaves for contraceptive property and associated estrogenic activities reveal that the specimen possesses significant pregnancy interceptive activity through restriction of implantation and there are also significant uterotrophic and hormonal effects involved. This specimen also demonstrated favorable effects on blood-lipid and carbohydrate profile, suggesting safe nature of the test substance. These noteworthy results motivated search for molecular species present in the plant, which might be responsible for the contraceptive and associated estrogenic effects. Through models generated in QSAR and structural homology studies, a compound \textit{viz.,} homostephanoline has been predicted to be appreciably estrogenic based on its calculated estrogenic activities from SAR models and structural similarities with E\textsubscript{2}. However, experimentation with this compound might further confirm the activity. Moreover, results of the pharmacological and biochemical studies further need to be evaluated using maximum number of animal sets to get better insight into the 'within-group' and 'across-group' variances.

Thus the studies demonstrate the utility of different molecular modeling processes and parameters involved therein in predicting molecular features responsible for bioactivity. The models generated from such studies can further aid in designing better active and target selective molecules, as well as for classifying bioactive molecules from natural resources. The latter part of this project signifies that the search for better contraceptive and hormone modulating agents, within the herbal resources should continue as this may yield new and promising lead compounds for future drug development.