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Summary and Conclusions

Cellular systems remain under a regular peril of intra- and extracellular stresses. Various genotoxic stresses and environmental factors have been found to be involved in causing perturbances in cellular homeostatic conditions. These disturbances may underlie as possible factors in the etiology of various diseases, which are still non-curable with the currently available knowledge and technological advancements in therapeutics. Proteostatic imbalance has been stipulated as a major risk factor in these diseases; like ageing, neurodegeneration and cancer. In the past, several attempts have been made to modulate the activities and functioning of the cellular protein quality systems and many small molecules have been identified with potential to upregulate proteolytic pathways and ameliorate proteotoxicity in neuronal cells under various pathological conditions. Similarly, suppression of proteasomal activities has shown tremendous potential to induce apoptotic cell death in cancer cells. The present study basically aims to identify putative molecular modulators of cellular protein quality control pathways.

5.1 SUMMARY

The studies presented in current research work have identified few small molecules that may alter the activity and functioning of cellular PQC machinery components and hence may provide possible therapeutic benefit in the treatment of many diseases that are associated with alterations in cellular protein quality control machinery.

5.2 CONCLUDING REMARKS

Lanosterol, a natural molecule and an intermediate of cholesterol biosynthesis pathway has shown promising effects on upregulation of autophagy pathway. It also upregulates and stabilizes a putative co-chaperone CHIP, which is known for its functions in chaperone mediated autophagy pathways. CHIP also functions as quality control E3 ubiquitin ligase and target misfolded proteins from the cytosol to proteasomal or lysosomal compartments for their degradation. Multiple diseases, which are combinedly termed as proteinopathies, are caused due to abnormal structural alterations or misfolding of cellular proteins. Hence, the effects shown by lanosterol could be helpful in ameliorating the toxicity generated due to the accumulation of abnormal cellular proteins.

The *in silico* and *in vitro* results presented in the study provide a putative therapeutic application of one of the precursors of cholesterol inside the human body. The results presented here propose a possible role of lanosterol in the suppression of protein aggregation mechanism, which is held responsible for a number of systemic and non-systemic diseases. A clear mechanism behind such a prominent activity of lanosterol and its proposed interaction with CHIP could be further elucidated by X-ray crystallography or NMR-based studies unraveling the fine structural details. Similar experimental studies on specific neuronal cell population will also be helpful in providing effectiveness of this drug on protein aggregates. Effects of lanosterol on multiple kinds of brain-associated functions in animal models of the different

neurodegenerative diseases are other concerns that must be looked at in future research works. These studies will benefit us by providing a clear insight into the interaction mechanisms and mode of action of such class of natural molecules that in turn will also help in identifying and characterizing other molecules with similar inhibitory potential over protein aggregation pathways. Several types of other natural molecules, which are either isolated from microbial sources or secondary metabolites that are extracted from plants, may provide new alternatives for the treatment of many protein misfolding associated disorders.

Cancer represents another class of diseases, in which dysregulation of cell cycle associated proteins may lead to uncontrolled cellular proliferation. A large number of factors, including intra- or extracellular stresses have been reported to cause tumor formation. Additionally, it has been proposed that inhibition of proteasomal activities may lead to activation of programmed cell death pathways. In the present study, an increased rate of cellular apoptosis via mitochondrial pathways has been observed in the cells under the treatment of a well-established non-steroidal anti-inflammatory drug ibuprofen. The detailed investigations revealed that ibuprofen-mediated apoptosis was induced due to mitochondrial abnormalities in membrane potential and release of cytochrome *c* into the cytoplasmic compartments.

The study would benefit us in devising new combinations of drugs that could be used in future therapeutic avenues. Previous studies, showing positive effects of ibuprofen on the anti-tumor properties of some other drugs when given in combination, also support the findings of the present study. However the effective inhibitory concentration of the drug needs to be further optimized to obtain the best possible beneficial effects. In addition, a detailed structural insight into the interaction of the drug with different subunits of the proteasome is needed to be explored with the help of advanced biophysical techniques and structural biology approaches, which will provide a better pharmacological understanding of such interactions between ligand and their target proteins. These interaction studies might also be helpful in designing and synthesizing new chemical compounds with better binding and inhibitory potential against the proteasomal subunits. *In vivo* studies based on various disease models of different types of cancer will also be helpful in profiling the pharmacological properties of these drugs. Additionally, future clinical studies could be aimed for patients suffering from cancers that may provide a clearer impact of such medications on the overall organism health.

5.3 CLOSING COMMENTS

The present study proposes novel therapeutic strategies, based on newly identified modulators of cellular protein quality control machinery, to target molecular pathways involved in the pathomechanism of many protein conformation associated diseases linked with the intracellular proteostasis disturbances.

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