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Delving through the wonders of green tea - Probing the dynamic selectivity of polyphenol Epigallocatechin gallate, a way-forward in the design of selective inhibitors for anti-apoptotic Bcl-2 proteins in cancer therapy.

Selective inhibition is a key focus in the design of chemotherapeutic compounds that can abrogate the oncogenic activities of major anti-apoptotic Bcl-2 proteins such as Bcl-2 and Bcl-xL. Although recent efforts have led to the development of highly selective BH3 mimetics, setbacks such as toxicities have limited their use in cancer therapy. Epigallocatechingallate (EGCG) is a non-toxic polyphenolic compound present in green tea widely reported to selectively target and inhibit Bcl2 and Bcl-xL, compared to other green tea phenols due to its unique gallate group. Therefore, molecular insights into mechanistic selectivity of EGCG via the gallate group could enhance the structure-based design of novel antagonists of anti-apoptotic Bcl-2 proteins. Herein, we investigate the interaction dynamics of EGCG at the hydrophobic grooves of Bcl-2 and Bcl-xL and the consequential effects on their BH4 domains since they reportedly mediate 'non-canonical' apoptotic resistance. Our findings revealed the crucial roles of Arg143 and Asp108 (Bcl-2), and Glu96 and Tyr195 (Bcl-xL) which specifically existed in high-affinity hydrogen interactions (CH—O, NH—O and OH—O) with the gallate group of EGCG, while the non-gallate group formed weak interactions. EGCG-bound proteins showed systemic perturbations of BH4 domains coupled with the burial and distortion of crucial surface-exposed residues such as Lys17 (Bcl-2) and Asp11 (Bcl-xL), which reportedly mediate non-canonical anti-apoptotic associations. Taken together, highly-specific interactions between the gallate group (of EGCG) and key residues at the hydrophobic grooves (of Bcl-2 and Bcl-xL) underlie the molecular basis of EGCG selectivity while simultaneous perturbations at their respective BH4 domains potentiate EGCG inhibitory potency. Accordingly, these in-depth structural and molecular insights will enhance the optimization and design of highly selective inhibitors that could suppress anti-apoptotic activities of Bcl2-family proteins with minimal toxicities.

HPC content

HPC was accessed through the lengau cluster of CHPC. The GCC 5.1.0 and openMPI 1.8.8 GNU compilers were accessed by loading their respective modules and the /apps/chpc/chem/amber/14 application code was used to access the Amber14 software package, which was used for MD simulations. Amber14 integrated modules such as ANTECHAMBER, LEAP were also used for system parameterization while the PTRJ and CPPTRAJ modules were used for analysis of trajectories and coordinates obtained. MD was carried out using the GPU accelerated PMEMD engine on a normal compute node of 48 cores (2 nodes).

Presenter Biography

As a focus-driven computational chemist, Fisayo Olotu has continued to explore the molecular world of disease pathogenesis via advanced computational techniques by carrying out independent and collaborative researches that focus majorly on 'seemingly' undruggable pathogenic players in pathways of prominent diseases such as cancer, HIV, malaria and tuberculosis, amongst many others. Currently in his second year of PhD, he has authored and co-authored peer-reviewed publications numbering 14. He had his BSc. degree in biochemistry and MSc. degree in Biochemistry, specializing in cancer research and molecular biology.

Primary author: Mr OLOTU, Fisayo (University of KwaZulu-Natal)

Co-authors: Prof. SOLIMAN, Mahmoud (UKZN); Mr AGONI, Clement (UKZN); Mr ADENIJI, Emmanuel (UKZN); Mrs ABDULLAHI, Maryam (UKZN)

Presenter: Mr OLOTU, Fisayo (University of KwaZulu-Natal)

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