I. INTRODUCTION

1.1 Background

The global incidence of cancer is undergoing a substantial escalation, as evidenced by the recorded 19.3 million recently diagnosed cases and approximately 10 million deaths in 2020 (Sung et al., 2020). If prevailing trends persist, encompassing a stable incidence rate and commensurate population growth, projections suggest a foreseen 54.9% increase in the worldwide prevalence with 28 million new cases by 2040 (GLOBOCAN, 2020). To avert this scenario, focused efforts should be directed towards the effective management of cancer treatments. Predominantly, radiotherapy, chemotherapy, or a combination thereof remain the established and extensively applied modalities for cancer management (Debela et al., 2021). However, their constrained capacity to selectively target cancer cells results in potential toxicity on normal cells, particularly those engaged in frequent cell division, thereby frequently contributing to patient mortality (van den Boogaard et al., 2022).

Currently, researchers are trying to develop targeted therapies that selectively focus on pathways exhibiting different regulation between cancer cells and normal cells. Some of the pivotal pathways include the excessive activation of Wnt/β-catenin signaling found in many types of cancer, which influences cell proliferation, differentiation and response to therapy (Anastas & Moon, 2013; Yuan et al., 2021). One of the central targets of the Wnt/β-catenin pathway is tankyrase 1. Tankyrase 1 holds significant appeal as anti-cancer target primarily because it exhibits higher expression levels in various cancer types compared to normal tissues (Lakshmi et al., 2017). It plays a role in Poly-ADP-ribosylation (PARsylation) where target proteins, which most of them are tumor suppressor, are subjected to degradation through ubiquitin-proteasome pathway. Therefore, tankyrase 1 inhibitors are gaining more attention to reduce cancer progression by antagonizing its role (Li et al., 2015; Kim, 2018). As of now, none of the tankyrase 1 inhibitors have successfully

completed clinical trials, resulting in the absence of any tankyrase 1 inhibitor being utilized in the clinical setting for patient treatment (Narwal, 2014).

In cancer research, *Saccharomyces cerevisiae* has been widely employed as a model in anti-cancer drug discovery (Cazzanelli et al., 2018). Generally, *S. cerevisiae* offers an inexpensive maintenance, simpler, and controlled environment to study specific aspects of cancer biology with a rapid doubling time compared to human cancer cells. Moreover, unlike humans, *S. cerevisiae* lacks both PARP and tankyrase homologs, making it possible to create a humanized yeast system (Yashiroda et al., 2010; Simon & Bedalov, 2004; Perkins et al., 2001). A humanized yeast model, a system engineered to express human genes in yeast, provides a direct approach to examine tankyrase 1 enzymatic activity and the effects of potential inhibitory compounds without interference from endogenous yeast enzymes (Engel et al., 2014; Kachroo et al., 2022). As a result, the yeast model system holds great value for the preliminary screening of tankyrase 1 inhibitors, offering promising prospects in uncovering novel and effective drugs for cancer therapy.

1.2 Objective

This research aims to analyze novel tankyrase 1 inhibitors as potential anti-cancer agents using humanized yeast cell-based bioassay. The sub-aims of this study are to validate the yeast cell-based screening system, screen the predicted compounds, and examine the effectiveness of the screened compounds in cancer cell lines using MTT assay.

1.3 Hypothesis

The tankyrase 1 inhibitors identified through the yeast cell-based screening system exhibit a significant reduction in cancer cell viability in the MTT assay when compared to the negative control (untreated).