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ORIGINAL ARTICLE

Quinazoline derivative from indigenous isolate, *Nocardiopsis alba* inhibits human telomerase enzyme

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Abstract

Aim: Aim of this study was isolation and screening of various secondary metabolites produced by indigenous isolates of soil Actinomycetes for human telomerase inhibitory activity.

Methods and Results: Extracellular extract from culture suspension of various soil Actinomycetes species were tested for telomerase inhibitory activity. The organism which produced telomerase inhibitor was identified by 16S rRNA gene sequencing. The active fraction was purified by HPLC and analysed by GC-MS to identify the compound. In GC-MS analysis, the active principle was identified as 3-[4′-(2″-chlorophenyl)-2′-thiazolyl]-2,4-dioxo-1,2,3,4-tetrahydro quinazoline. The G-quadruplex stabilizing ability of the compound was checked by molecular docking and simulation experiments with G-quadruplex model (PDB ID-1L1H). The selective binding ability of the compound with G-quadruplex over Dickerson–Drew dodecamer DNA structures showed that the compound possess high selectivity towards G-quadruplex.

Conclusions: Quinazoline derivative isolated from an indigenous strain of *Nocardiopsis alba* inhibited telomerase. Molecular docking and simulation studies predicted that this compound is a strong stabilizer of G-quadruplex conformation. It also showed a preferable binding to G-quadruplex DNA over normal DNA duplex.

Significance and Impact of the Study: This particular compound can be suggested as a suitable compound for developing a future anticancer drug. The selectivity towards G-quadruplex over normal DNA duplex gives a clue that it is likely to show lower cytotoxicity in normal cells.

Introduction

Currently chemotherapy is regarded as one of the most effective way to treat cancer. An extensive research in this area has been carried out in the past few decades to understand the basic mechanism involved in many cancer types. Better understanding about human cancers and their subtypes have revolutionized the effectiveness of chemotherapeutic approaches. The extended lifespan of individual cancer cells leads to the expansion of a tumour mass. Immortalization of the altered cells is one of the initial events happening in tumorigenesis. In cancer cells, immortality is achieved through the expression of telomerase enzyme. Telomerase is basically a ribonucleoprotein complex which replenishes the telomeric region which gets eroded during every step of mitotic division (Shay and Wright 2000). Telomerase enzyme synthesize repeated DNA sequences ($TTAGGG_n$) at the chromosome ends and this extended DNA will get entangled with a group of proteins called 'shelterin' which forms a cap to telomeric region. This capping protects chromosomes from eliciting DNA damage response followed by apoptosis (Moyzis *et al.* 1988; Smogorzewska and de Lange 2004; de Lange 2005; Palm and de Lange 2008).