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Telomerase inhibitory effects and anti-proliferative properties of onion and other natural spices against cancer cells

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ABSTRACT

The objectives of current study were to find the potential telomerase inhibitors from spices and to investigate their anticancer properties. The in vitro inhibitory effects of 28 spices against telomerase activity of HL-60 cells were systematically studied using polymerase chain reaction (PCR) based telomeric repeat amplification protocol, the PCR products were determined using native polyacrylamide gel electrophoresis. Telomerase inhibitory activity was evaluated by comparing DNA ladders. Telomerase inhibitory samples were further tested for anti-proliferation effects against gastric cancer cells SNU-1 using MTT assay. Hexane extract of onion, hexane extract of chili, ethyl acetate extract of chili, water extract of chili, and water extract of parsley exhibited strong telomerase inhibiting activity at the concentration of 10 μg/mL. Further anti-proliferation study indicated that hexane and ethyl acetate extracts of onion and ethyl acetate extract of chili at the concentration of 10 μg/mL showed 51.9%, 43.7% and 22.2% inhibitory rate against gastric cancer cells SNU-1, respectively; while the water extracts of chili and parsley did not show cancer cell proliferation inhibitory effect. The hexane extract of onion exhibited both telomerase inhibitory effect and cancer cell proliferation inhibitory effect with IC_{50} value at 14.18 μg/mL. Onion deserves to be further studied, it has a potential to be developed into an anticancer agent targeted on telomerase.

1. Introduction

It has been widely accepted that telomeres protect chromosome ends since Blackburn (1991) found that the damaged chromosomes lacking telomeres undergo fusion, rearrangement and translocation. Previous studies verified that telomere lengths of somatic cells are progressively shortened with each cell division both in vivo and in vitro (Harley, Futcher, & Greider, 1990; Lindsey, McGill, Lindsey, Green, & Cooke, 1991). Telomerase was found to be a ribonucleoprotein that has a function to synthesize and direct the telomeric repeats onto the 3′ end of existing telomeres using its RNA component as a template in the eighties of last century (Morin, 1989). Later on telomerase activity was shown to be specifically expressed in immortal cells, cancer and germ cells (Kim et al. 1994; Shay & Wright, 1996), where telomerase

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compensates for telomere shortening during cell divisions and thus stabilizes telomere length. These observations make scientists reach a common view that telomere length may function as a "mitotic clock" to sense the number of DNA replication and eventually signal replicative senescence or programmed cell death once a critical telomere length is achieved. Hence, expression of telomerase activity in cancer cells could be an essential step for tumor development. Kim et al. (1994) developed a sensitive and efficient polymerase chain reaction (PCR)-based telomerase activity detection method, telomeric repeat amplification protocol (TRAP). The validated TRAP protocol has made possible large-scale detection of telomerase activity in both scientific research and clinical diagnose. Based on the TRAP technique, positive expression of telomerase has been detected in over 85% of all tumors tested spanning more than 20 different types of cancers (Shay & Bacchetti, 1997; Nelson, 1996).

In order to find the potential inhibitor against tumor telomerase activity, different ways have been explored to inhibit telomerase activity and interfere with tumor development during the past two decades. Most of the scientists have concentrated their energy on the biochemistry aspect of telomerase and quit a few studies were carried out on medicinal plants. However, the most inspiring achievement is that certain natural products or compounds derived from plants have been found to possess telomerase inhibitory effects. For instance, mistletoe (Lyu, Choi, & Park, 2002) and tea catechins (Naasani, Seimiya, & Tsuruo, 1998) have shown telomerase inhibitory activity. As a special category of natural products, certain spices have been found to own anti-tumor effects from in vitro and in vivo studies. However, no research was performed to screen potential telomerase inhibitors from spices to date. In light of such context, telomerase inhibitory properties of collected spices against human cancer cells were firstly investigated in present study.

2. Materials and methods

2.1. Chemicals and reagents

Dimethyl sulphoxide (DMSO), acrylamide, N-N-methylene-bis-acrylamide, 2-hydroxyethyl piperazine-N-ethanesulfonic acid (HEPES), phenyl methyl sulfonyl fluoride (PMSF), 3-[(3-cholamidoproyl)-dimethylammonio]-1-propane sulfonate (CHAPS), ethyleneglycolbis (aminoethlether)-tetraacetic acid (EGTA), diethyl pyrocarbonate (DEPC) were purchased from Sigma (St. Louis, MO, U.S.A.). RNase inhibitor was purchased from TaKaRa (TaKaRa, Seoul, South Korea). Deoxynucleotide triphosphate (dNTP) and *Taq* DNA polymerase were supplied by Bioneer Cooperation (Taejon, South Korea). All other reagents were of analytical grade which were delivered by Duksan Pure Chemical Co., Ltd. (Ansan, South Korea). Purified water was obtained from a Milli-Q (Millipore, Bedford, MA, U.S.A.) water purification system.

Table 1 – Telomerase inhibitor screening of spices using telomeric repeat amplification protocol-polymerase chain reaction assay.

Common name	Scientific name of plant	Family name	Parts used	Source	H	E	W
Garlic	*Allium sativum* L.	Liliaceae	Stem	Korea	–	–	–
Welsh onion	*Allium fistulosum* L.	Liliaceae	Stem	Korea	–	–	–
Onion	*Allium cepa* L.	Liliaceae	Stem	Korea	+	+	–
Ginger	*Zingiber officinale* Rosc.	Zingiberaceae	Rhizome	Korea	–	–	–
Chilli	*Capsicum annuum* L.	Solanaceae	Fruit	Korea	+	+	+
Laurel	*Laurus nobilis* L.	Lauraceae	Bark	China	–	+	+
Bay leaf	*Laurus nobilis* L.	Lauraceae	Leaf	Turkey	–	–	–
Cinnamon	*Cinnamomum zeylanicum*	Lauraceae	Bark	France	–	–	+
Parsley	*Petroselinum sativum* Hoffm.	Apiaceae	Leaf	France	–	–	+
Common fennel	*Foeniculum vulgare* Mill	Apiaceae	Seed	China	–	–	–
Star anise	*Foeniculum vulgare*	Illiciaceae	Fruit	China	–	–	–
Cumin	*Cuminum cyminum*	Apiaceae	Fruit	China	–	–	–
Black pepper	*Piper nigrum* L.	Piperaceae	Fruit	China	–	–	–
Cloves	*Syzygium aromaticum* L.	Myrtaceae	Flower bud	China	–	–	+
Mint	*Mentha arvensis* L.	Lamiaceaee	Leaf	China	–	–	–
Coriander	*Coriandrum sativum* L.	Apiaceae	Leaf	China	–	–	–
Nutmeg	*Myristica fragrans* Houtt	Myristicaceae	Fruit	China	–	–	–
Rosemary	*Rosemarinus officinalis*	Labiatae	Leaf	France	–	–	–
Basil	*Ocimum basilicum* L.	Lamiaceae	Whole herb	France	–	–	–
Sage	*Salvia officinalis* L.	Asteraceae	Whole herb	France	–	–	–
Tarragon	*Artemisia dracunculus* L.	Lamiaceae	Leaf	France	–	–	–
Oregano	*Origanum heracleoticum*	Lamiaceae	Leaf	France	–	–	+
Perilla seed	*Perilla frutescens*	Lamiaceae	Seed	China	–	–	–
Thyme	*Thymus vulgaris*	Lamiaceae	Leaf	China	+	–	+
Dill	*Anethum sowa*	Apiaceae	Fruit	India	–	–	–
Caraway	*Carum carvi*	Apiaceae	Seed	China	–	–	–
Celery seed	*Apium graveolens* L.	Apiaceae	Seed	China	–	–	–
Poppy seed	*Papaver somniferum* L.	Papaveraceae	Seed	Korea	–	–	–

–, negative results; +, positive results; w, weak telomerase inhibitory activity. H, hexane extract; E, ethyl acetate extract; W, water extract.