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Effects of Current Chemotherapy Drugs and Natural Agents in Treating Non–Small Cell Lung Cancer

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ABSTRACT

The fact that lung cancer is the most common cancer to cause death makes it a desirable condition for study and potential improvement of therapeutic treatment choices. Lung cancer is frequently treated with surgery, radiation, chemotherapy, targeted therapies, and immunotherapy alone or in combination. Chemotherapy-based regimens appear to have achieved a therapeutic plateau, yet these treatment modalities may have varied side effects. As a result, this problem needs to be addressed and hopefully resolved with the help of efficient, better-tolerated medicines. Recent developments have made it possible for biologists to more thoroughly explore the potential application of natural chemicals for the control or therapy of many malignant conditions. Natural compounds have been the foundation of chemotherapy for the past 30 years. However, only a small number of substances have been studied in cancer patients, and there is only scant information about their clinical efficacy. Here, we evaluate the evidence for the therapeutic benefits of natural substances (such as Wortmannin and Roscovitine, Cordyceps militaris, Resveratrol, OSU03013, Myricetin, Berberine, and Antroquinonol) and current chemotherapy medicines, including those against non-small cell lung cancer. We suggest using these medicines in combination with chemotherapeutic treatments for patients with advanced and/or refractory solid tumours based on the literature review.

KEYWORDS: *NSCLC; Chemotherapy; Solid tumors; Natural compounds; Surgery; Radiation*

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INTRODUCTION

Lung cancer is the most common cause of death from cancer overall [1, 2]. It is responsible for 1.4 million (or 17.7%) of all cancer deaths per year. The most prevalent form of lung cancer, lung adenocarcinoma, affects both smokers and nonsmokers as well as people under the age of 45. About 30% of initial lung tumours in male smokers and 40% in female smokers are caused by adenocarcinoma. These figures are close to 60% for men and 80% for women among non-smokers. Asian populations are also more likely to develop this specific type of lung cancer (www.cancer.gov). In Taiwan, there has been an increase in the number of lung cancer deaths.

Despite advances in development of new treatment modalities, the overall 5-year survival rate has only slightly increased over 2.5 decades, remaining at approximately 16% [4, 5]. Early diagnostic procedures and hits, and effective screening for nonsmall cell lung cancer (NSCLC) is still lacking [6]. Unfortunately, many patients with lung cancer are diagnosed at a late stage (i.e. stage III b or IV), and there is no curative treatment for such an advanced stage [7]. In Taiwan, liver, lung, stomach, colon, and oral cavity cancers are the five leading cancers responsible for cancer deaths among males; while lung, liver, cervix uteri, breast, and stomach are the five leading cancers responsible for cancer deaths among females [8]. Smoking, drinking alcohol, and chewing betel nut are three significant lifestyle factors linked to an elevated risk of cancer in Taiwan. According to a dose-response analysis, smoking increases the risk of developing lung, hepatoma cellular carcinoma, oral cavity, neural progenitor cells, esophageal, urinary bladder, and cervical cancers [9–12]. Similar to this, tobacco use is one of the primary etiological factors in western countries,

accounting for 85% of all incidences of lung cancer [13]. A higher dietary intake of fruits or vegetables is associated with a lower risk of lung cancer, according to studies on the role of a person's diet as a potential risk factor for the disease.

Related Work:

Wang, Kai; Zhang, Chao; Bao, Jiaolin; Jia, Xuejing; Liang, Yeer; Wang, Xiaotong; Chen, Meiwan; Su, Huanxing; Li, Peng; Wan, Jian-Bo; He, Chengwei: Famous natural substances berberine (BBR) and curcumin (CUR) both display significant anticancer properties through various molecular mechanisms. However, neither CUR nor BBR have a very strong anticancer effect. As a result, we looked at the chemopreventive potential of combining CUR and BBR to treat breast cancer. The findings demonstrated that CUR and BBR reduced the proliferation of MCF-7 and MDA-MB-231 breast cancer cells more effectively when used together than when used separately. Additional research verified that the co-treatment of these two drugs resulted in greater levels of apoptosis and autophagic cell death, which had synergistic anti-breast cancer effects (ACD). Apoptosis was produced by cotreatment in a caspase-dependent manner through activating ERK pathways. Our findings also showed that co-treatment with CUR and BBR significantly increased JNK and Beclin 1 phosphorylation while lowering Bcl-2 phosphorylation. JNK inhibition by SP600125 significantly lowered LC3-II and Beclin1, restored phosphorylated Bcl-2, and lessened the cytotoxicity brought on by the two substances when used together. These findings strongly suggested that the co-administration of CUR and BBR to breast cancer cells resulted in the production of ACD by the JNK/Bcl-2/Beclin1 pathway. This research sheds light on how curcumin and berberine might be used in combination for the chemoprevention and treatment of breast cancer.

Po-Cheng Chiang,, Ssu-Chia Lin, Shiow-Lin Pan, Ching-Hua Kuo, I-Lin Tsai, Mao-Tien Kuo, Wu-Che Wen, Peini Chen, Jih-Hwa Guh: Two serine/threonine protein kinases, AMP-activated protein kinase (AMPK) and mammalian target of rapamycin (mTOR), are in charge of regulating translation and maintaining cellular energy balance, respectively. There is evidence that these two kinases could be used as cancer treatment targets for hepatocellular carcinoma (HCC). With regard to both HBV DNA-positive and -negative HCC cell lines, antroquinonol, which was extracted from Antrodia camphorate, a well-known Traditional Chinese Medicine for the treatment of liver illnesses, shown potent anticancer activity. HepG2 is the most effective against HCCs, followed by HepG2.2.15, Mahlavu, PLC/PRF/5, SK-Hep1, and Hep3B. When liberated from double-thymidine-block synchronisation, antroquinonol fully eliminated cell-cycle progression and triggered apoptosis. The considerable reversal of antroquinonol-mediated effects by compound C, a specific AMPK inhibitor, points to the critical function of AMPK. Additionally, the reduced mitochondrial content and loss of mitochondrial membrane potential demonstrated the mitochondrial stress brought on by antroquinonol. In conclusion, the evidence indicates that antroquinonol has anticancer properties against HCCs via activating AMPK and inhibiting the mTOR translational pathway, which results in G1 arrest of the cell cycle and consequent cell apoptosis.

Hsien-Chun Lin, Mei-Hsiang Lin, Jiahn-Haur Liao, Tzu-Hua Wu, Tzong-Huei Lee, Fwu-Long Mi, Chi-Hao Wu, Ku-Chung Chen, Chia-Hsiung Cheng, and Cheng-Wei Lin: The rare fungus Antrodia camphorata produces antroquinonol, a ubiquinone derivative with broad-spectrum bioactivities. However, it is still unknown how ANQ will affect colon cancer's characteristics resembling cancer stem cells. In this investigation, we discovered that ANQ prevented colon cancer cells from growing. On HCT15 and LoVo, ANQ's 50% growth inhibitory concentrations (GI50) were 34.8 0.07 M and 17.9 0.07 M, respectively. Additionally, colon cancer cells' motility, invasion, and creation of tumorspheres were inhibited by ANQ. A-catenin/T-cell factor (TCF) signalling was down regulated and pluripotent and cancer stem cell-related genes were suppressed by ANQ in a mechanistic manner. Additionally, it was shown that the phosphatidylinositol-3-kinase (PI3K)/AKT/-catenin signalling axis is essential for controlling the expression of pluripotent genes, whereas ANQ's inhibition of PI3K/AKT suppressed the production of -catenin and its downstream targets. The possibility for ANQ and PI3K interaction was discovered using molecular docking. Using PI3K/AKT/-catenin signalling as a target, our data demonstrate for the first time how the bioactive component of A. camphorata, ANQ, reduces stem cell-like characteristics. An effective cancer preventative for colon cancer may be ANQ.

Zhi Hong Wanga, Kyoung Ah Kanga, Rui Zhanga, Mei Jing Piaoa, Su Hyun Jo b, Ju Sun Kimc, Sam Sik Kangc, Jong Sung Lee d, Deok Hoon Park d, Jin Won Hyuna: By measuring the scavenging power of reactive oxygen species (ROS) and the activities of antioxidant enzymes, we assessed the cytoprotective impact of myricetin on cells injured by oxidative stress. Myricetin demonstrated

the 1,1-diphenyl-2-picrylhydrazyl (DPPH) radicals' ability to scavenge intracellular ROS. Myricetin also reversed the effects of hydrogen peroxide (H2O2) on cellular antioxidant defence enzymes such superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), restoring their activity and protein expression. Myricetin was discovered to prevent the DNA damage indicated by suppression of DNA tail and it decreased nuclear phospho-histone H2A.X expression, both of which are markers for DNA strand breakage. H2O2-induced cellular DNA and lipid damages were also observed. Additionally, membrane lipid peroxidation was reduced, as evidenced by the reduction of TBARS production and diphenyl-1-pyrenylphosphine fluorescence intensity (DPPP). These findings imply that myricetin protects cells from H2O2-induced cell damage by preventing the production of ROS and stimulating the activity of antioxidant enzymes.

TAO ZHANG, GUANG-BIN CUI, JIAN ZHANG, FENG ZHANG, YONG-AN ZHOU, TAO JIANG and XIAO-FEI LI: Ionizing radiation is not as damaging to non-small cell lung cancer (NSCLC) cells as it is to other cancers (IR). The phosphatidylinositol 3-kinase (PI3-K) family of lipid kinases mediates biological processes such cell growth, proliferation, and DNA repair, all of which may aid in radioresistance. We investigated if PI3 kinase inhibition could improve NSCLC cell sensitivity to radiation. The findings demonstrated that wortmannin, a PI3 kinase inhibitor, pretreated NSCLC A549 and H1650 cells in a dose-dependent manner that increased G2/M arrest and death, hence reducing colony formation and radiosensitizing the cells. Increased loss of mitochondrial membrane potential (MMP) and cytochrome c leakage to the cytoplasm were seen in conjunction with the accelerated apoptosis. . Additionally, pretreatment with wortmannin markedly boosted caspase-3 activation, which was connected to the suppression of the X-linked inhibitor of apoptosis protein (XIAP). Wortmannin's radio sensitizing action and the level of phosphorylated PKB/Akt were both inhibited. Additionally, wortmannin decreased the activity of DNA-PKcs, a component of DNA double-strand break (DSB) repair, down-regulating its expression. This prevented DSBs from rejoining, as seen by an increase in the amount of -H2AX 24 hours after IR. Together, these findings show that wortmannin inhibits DNA-PKcs and PI3K/Akt survival signalling in NSCLC cells, acting as a potent radio sensitizer. These findings raise the possibility that PI3 kinase inhibitors may be a new means of overcoming NSCLC cells' resistance to IR-induced apoptosis.

- **Soo-Yeon Park, Young Mee Kim, Hongryull Pyo:** A subgroup of patients with non-small cell lung cancer (NSCLC) treated with EGFR inhibitors experienced remarkable improvements, and they have also been proven to improve the effects of ionising radiation (IR).We looked into the radio sensitization of NSCLC cells caused by the EGFR inhibitor gefitinib, which is taken orally by NSCLC patients.NCI-H460 and VMRC-LCD but not A549 cells were radio sensitized by gefitinib in clonogenic survival experiments carried out in three NSCLC cell lines. NCI-H460 and VMRC-LCD cells were exposed to IR following gefitinib pretreatment, whereas A549 cells were not. Additionally, gefitinib prevented, but did not stop, the activation of ataxia telangiectasia mutant (ATM) after IR exposure in NCI-H460 and VMRC-LCD cells. In both NCI-H460 and A549 cells, an ATM-specific inhibitor enhanced the number of multinucleated cells brought on by IR. Pretreatment with gefitinib prevented NCI-H460 but not A549 cells from gradually losing gH2AX foci in relation to time following IR exposure. After receiving gefitinib + IR treatment, COX-2 suppression in A549 cells led to multinucleated cells and radio sensitization. On the other hand, after the same treatment, COX-2 overexpression in NCI-H460 cells reduced the development of multinucleation and radio sensitization. Our findings imply that gefitinib radio sensitizes NSCLC cells by preventing ATM activity and thus triggering mitotic cell death, and that gefitinib is inhibited by COX-2 overexpression in NSCLC cells.

W. L. Wendy Hsiao, Liang Liu: Herbal remedies based on traditional Chinese medicine have become more widely accepted in recent years, and pharmaceutical companies are pursuing them as valuable sources for new medication development. Traditional Chinese medicine (TCM) has been used for many years in China and other countries to treat malignancies. Herbal medications are typically inexpensive, readily available, and exhibit relatively minimal toxicity or adverse effects in therapeutic settings. The biggest barriers to the globalisation of TCM, despite the enormous interest and rising demand, are the lack of good evidence-based research and the lack of standardisation of herbal products. As analytical tools and procedures have advanced recently, TCM research has greatly increased. This analysis of TCM's application in the treatment of cancer is broken up into two sections. The first section gives an overview of the principles, methods, and developments in TCM-based cancer therapy. The

second section outlines what is known currently about how TCM-derived substances work as anticancer medications.

Alan L. Harvey, Ian A. Cree: The majority of anticancer medications have been derived from natural products, and attempts are still being made to discover new lead compounds by examining the chemical diversity that nature provides. High throughput screening assays have evolved from bioassay test procedures employing both cell-based and molecular techniques. Examples of recent breakthroughs using three-dimensional cultures and cancer stem cells are shown, along with a summary of the many methods for detecting impacts on cell survival and proliferation. The development of cell-based reporter assays has also allowed for a more direct examination of the impact on particular physiological pathways. Several distinct protein kinases as well as microtubules and associated proteins are the targets of the molecular assays.

Zhi Hong Wanga, Kyoung Ah Kanga, Rui Zhanga, Mei Jing Piaoa, Su Hyun Jo b, Ju Sun Kimc, Sam Sik Kangc, Jong Sung Lee d, Deok Hoon Park d, Jin Won Hyun: By measuring the scavenging power of reactive oxygen species (ROS) and the activities of antioxidant enzymes, we assessed the cytoprotective impact of myricetin on cells injured by oxidative stress. Myricetin demonstrated the 1,1-diphenyl-2-picrylhydrazyl (DPPH) radicals' ability to scavenge intracellular ROS. Myricetin also reversed the effects of hydrogen peroxide (H2O2) on cellular antioxidant defence enzymes such superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), restoring their activity and protein expression. Myricetin was discovered to prevent the DNA damage indicated by suppression of DNA tail and it decreased nuclear phospho-histone H2A.X expression, both of which are markers for DNA strand breakage. H2O2-induced cellular DNA and lipid damages were also observed. Additionally, TBARS production and fluorescence intensity of membrane lipid peroxidation were inhibited.

Chia-Chun Yua, Po-Cheng Chianga, Pin-Hsuan Lua, Mao-Tien Kuob, Wu-Che Wenb, Peini Chenc, Jih-Hwa Guha: A malignant pancreatic tumour is called pancreatic cancer. In more than 90% of pancreatic adenocarcinomas, K-ras has a mutation and is constitutively activated. It is critical to find an effective strategy for the treatment of pancreatic malignancies. An isolated ubiquinone derivative from a camphor tree is called antroquinonol. On the other hand, K-ras expression and phosphorylation both considerably increased. The oimmunoprecipitation experiment revealed a markedly increased connection between K-ras and Bcl-xL, which was suggestive of apoptotic cell death. In addition, apoptosis, autophagic cell death, and accelerated senescence were all brought on by antroquinonol, which was at least partially explained by the up-regulation of p21Waf1/Cip1 and K-ras. In conclusion, the evidence points to the possibility that antroquinonol causes anticancer activity in human pancreatic tumours via inhibiting the PI3-kinase/Akt/mTOR pathways, which in turn suppresses cell cycle egulators.p21Waf1/Cip1 and K-ras were upregulated, which, at least in part, accounted for the observed phenomenon. In conclusion, the evidence points to the possibility that antroquinonol causes anticancer activity in human pancreatic tumours via inhibiting the PI3-kinase/Akt/mTOR pathways, which in turn suppresses cell cycle regulators. The cell cycle is stopped in the G1 phase due to the translational inhibition, which leads to a mitochondrial-dependent death. Additionally, the anticancer effect of antroquinonol is also explained by autophagic cell death and hastened senescence.

Existing System/Open Issues:

Recent developments have made it possible for biologists to more thoroughly explore the potential application of natural chemicals for the control or therapy of many malignant conditions. Natural compounds have been the foundation of chemotherapy for the past 30 years. However, only a small number of substances have been studied in cancer patients, and there is only scant information about their clinical efficacy. Here, we evaluate the evidence for the therapeutic benefits of natural substances (such as Wortmannin and Roscovitine, Cordyceps militaris, Resveratrol, OSU03013, Myricetin, Berberine, and Antroquinonol) and current chemotherapy medicines, including those against non-small cell lung cancer.

Negative comments:

Peripheral neuropathy or other nerve problems, such as numbness, tingling, and pain. Skin and nail changes such as dry skin and color change. Urine and bladder changes and kidney problems.

The toxic side effects, the development of resistance to the chemical agents, and the need for other forms of treatment, in combination with chemotherapy, in order to cure the patient.

Mouth, tongue, and throat problems such as sores and pain with swallowing.

Conclusion:

Patients with NSCLC in the early stages often have two treatment options: surgery or radiotherapy. Chemotherapy has demonstrated some efficacy when

administered alone to individuals with stage IV illness, as well as when combined with radiotherapy to treat patients with locally progressed disease and those with early-stage NSCLC prior to surgery. Based on clinical research and the findings of meta-analyses, platinum medicines are still regarded as being of utmost importance, despite their documented toxicity and inherent resistance. Chemotherapy's poor efficacy and significant toxicity have led to a lot of scepticism about this strategy for a long time because just a minor improvement in survival rates was noticed. Natural substances, meantime, have been utilised to treat a variety of illnesses and are expanding as a key field of study for the development of new drugs. It may be feasible to control and manage cancer by combining natural medicines with chemotherapy drugs in patients with advanced and/or refractory solid tumours. This would lower the toxicity risk brought on by chemotherapy.

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