IJHS

Editorial

Liposomal thymoquinone, a novel drug formulation: Hope for lung cancer treatment

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WEBSITE: ijhs.org.sa
ISSN: 1658-3639
PUBLISHER: Qassim University

Lung cancer is ranked second in the occurrence of cancer after breast cancer and first leading cause of cancer-related death globally. According to GLOBOCAN 2020, more than 2.2 million cases of lung cancer were registered, making up to 18% of total cancer deaths in the year 2020 worldwide. The continuous increase in the incidence of lung cancer has also been reported in Saudi Arabia, as it was placed 7th and 5th in total cancer cases and mortality, respectively.[1] As evident from several studies, the incessant upsurge in the consumption of tobacco among males and females in the countries such as India, China, and Saudi Arabia is the major source in the prevalence of lung cancer.[2,3] Several studies revealed that the smokers have 20-fold higher risk in comparison to non-smokers, and 90% of lung cancer cases are reported due to the exposure of tobacco. Benzo[a]pyrene (BaP), a polycyclic hydrocarbon found in tobacco smoke, is one of the leading causes in the etiology of lung cancer.[4,5] The BaP makes the DNA adduct formation followed by the promotion and progression of cancer after metabolically activated into 7,8-diol-9, 10-epoxide reacting with DNA primarily.[6] Therefore, the BaP has been used in all three stages (initiation, promotion, and progression) of the lung cancer model in laboratory animals.[7]

The visible nodules with broad appearance of lobes are developed in the lungs of rodents after the exposure of BaP through oral route which primes the overexpression of cytosolic receptor known as aryl hydrocarbon (AhR).[8] Then, the activated AhR makes the complex with the ARNT following translocation into the nucleus. As a result, the complex of activated AhR/ARNT induces the transcription of genes following binding to particular DNA recognition locations upstream of AhR-mediated genes.[9] The initiation of carcinogenesis event involves AhR-associated upregulation of cytochrome p450 (cyp450) enzymes. It metabolizes BaP into an intermediate mutagenic epoxide by which the DNA adducts formation is formed readily. Therefore, these adducts are supposed to be associated with polycyclic aromatic hydrocarbons (PAH)-mediated process of carcinogenesis leading to DNA mutations followed by malignant transformation.[10,11]

Keeping these views into considerations, AhR could be potential novel target for the treatment of lung cancer. Anticancer drugs are usually afflicted with toxic manifestations at required concentration of doses to control the process of carcinogenesis at various stages.[12] It is evident from several epidemiologic studies that various natural foods contained within the diets may decrease the risk or delay the progression of various diseases such as cancer, cardiovascular disease, and diabetes.[13] The idea of using natural foods to minimize the risk of various types of cancer dates back many decades.[14] It is believed that 33% of total mortality occurred due to the cancer could be prevented by including the high amounts of natural foods in the diet.[15-18] Remarkably, it is nearly 50% of the drugs which made available in the market in the past 30 years were either derived directly from plants or chemically modified.[19] Multiple studies have shown the role of naturally occurring bioactive dietary constituents as AhR agonists. The low toxicity of these secondary metabolites, that is, tetrandrine, norisoboldine, berberine, sinomenine, resveratrol curcumin, thymoquinone (TQ), etc., and interaction with AhR makes them interesting candidates for research.[19] TQ, one of the major active constituents of black seeds (*Nigella sativa*), has been reported to be potential agonist of AhR. Evidently, several studies have reported TQ to be a promising anti-cancer therapeutic compound, affect multiple signaling pathways that control cell proliferation, apoptosis, and metastasis.[20]

Moreover, irrespective of retaining broad therapeutic potential, the usage of TQ has limited due to its poor solubility in an aqueous medium. Keeping this view into consideration, the preparation of appropriate formulation of TQ is required to broaden its usage. It can also enhance the bioavailability and effectiveness as well, by the incorporation of TQ in liposome-based nanoparticles. However, the toxicity of plant extracts or their secondary metabolites are not appropriately investigated, as there is erroneous perception that herbal medicines are devoid of adverse or toxic side effects. Therefore, the toxicity of TQ should be explored appropriately as of any synthetic drug.[21,22]

The detailed analyses are required to determine the potential of TQ *in vitro* as well as *in vivo* AhR activated lung cancer models using PAHs. To prepare the effective formulations of TQ against cancer, different form of liposomes could be characterized with varying concentration of TQ. Each formulation should be screened against AhR-induced different types of lung cancer cells. As AhR is associated with the regulation of multiple signal transduction pathways such as FAK/Src, PI3K/Akt, transforming growth factor-B, and NF-kB, the effect of each formulation is required by determining the changes in the genes of these signaling pathways. The development of least toxic, more convenient, and effective novel formulation of TQ will certainly decrease the number of lung cancer cases worldwide.

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