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Host-specific endophytes of *Momordica charantia*: A promising source for affordable lung cancer therapeutics

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ABSTRACT

Endophyte-host interactions lead to the production of various bioactive compounds. Thus, endophytes from a medicinal plant such as *Momordica charantia,* can be promising candidates for producing pharmacological compounds. Our study therefore aims to evaluate these endophytes as sustainable sources of potential low-cost lung cancer drugs. We determined the endophytes associated with *M. charantia* (fruit and leaf) and assessed anti-inflammatory, antioxidant and antiproliferative potential against NCI-H23 lung cancer cells. LC-Q-TOF-MS of the endophyte extracts was conducted to determine the metabolite profile.

Leaf endophyte *F. circinatum* showed anti-inflammatory (114.29 %), antioxidant (IC_{50}=27.39 μg/ml) and antiproliferative activity (IC_{50}=98.62 μl/ml) with decreased *Beclin1* expression (autophagy regulator) in NCI-H23 cells. It produced five anticancer compounds namely linamarin, xestoaminol C, phytosphingosine, cucurbitacin E and margarolic acid. Fruit endophyte *E. fergusonii* also showed significant antiproliferative potential (IC_{50}=170.8 μl/ml) with upregulated apoptosis regulator *Bcl2* expression. It produced compounds such as eplerenone, kuguacin C and H. With the production of triterpenoids momordicine I, cucurbitacin E and kuguaglycoside A, leaf endophyte *A. faecalis* showed antioxidant potential (IC_{50}=29.65 μg/ml) but limited antiproliferative activity. This is the first report of endophytes-mediated biosynthesis of host-specific compounds in *M. charantia* including momordicine I, cucurbitacin E and kuguacins, which are known to have anti-cancer properties. Thus, these medicinal plant endophytes can be low-cost sustainable candidates with anti-cancerous potential, especially against lung cancer.

1. Introduction

Cancer is one of the leading causes of death in 127 countries with lung cancer being its most lethal form. According to GLOBOCON 2020, lung cancer remains a leading cause of cancer-related deaths with 1.8 million mortality and 19.3 million new cases globally (about 18 %) (Sung et al., 2021). In India, it accounted for about 5 % of the total cancer deaths with 0.1 million new cases in 2022 (Sathishkumar et al., 2022). Currently, various chemotherapeutic agents are available commercially such as gemcitabine, docetaxel, paclitaxel, vinorelbine, topotecan, irinotecan, carboplatin and oxaliplatin (Iqbal et al., 2017; Kusari et al., 2009; Pimentel et al., 2011). These drugs are reported to increase the survival of the cancer patient for up to one year. However, due to the divergent nature of every cancer case, a definite course of action is next to impossible. The major limitation is the number of therapy dropouts due to drug-related side effects, lack of interest or cost, which lead to the development of resistant cancers (Avancini et al., 2020). Moreover, tumour heterogeneity and increased drug resistance may cause severe complications during cancer treatment (Goyal et al., 2017). Thus, the search for drug alternatives in the past decades has led to the discovery and development of novel bioactive compounds from natural sources.

Medicinal plants are one of the major sources of these compounds and contribute to about 80 % of the total natural bioactive compound-based drugs (Singh and Dubey, 2015). However, due to *in-planta* synthesis in low amounts, organ-specific localization, ecological implications as well as a rapidly increasing market, their limited

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