Morindone From *Morinda Citrifolia* as a Potential Antiproliferative Agent Against Colorectal Cancer Cell Lines

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Abstract

There is an increasing demand in developing new, effective, and affordable anti-cancer against colon and rectal. In this study, our aim is to identify the potential anthraquinone compounds from the root bark of *Morinda citrifolia* to be tested *in vitro* against colorectal cancer cell lines. Eight potential anthraquinone compounds were successfully isolated, purified and tested for both *in-silico* and *in-vitro* analyses. Based on the *in-silico* prediction, two anthraquinones, morindone and rubiadin, exhibit a comparable binding affinity towards multitargets of β-catenin, MDM2-p53 and KRAS. Subsequently, we constructed a 2D interaction analysis based on the above results and it suggests that the predicted anthraquinones from *Morinda citrifolia* offer an attractive starting point for potential antiproliferative agents against colorectal cancer. *In vitro* analyses further indicated that morindone and damnacanthal have significant cytotoxicity effect and selectivity activity against colorectal cancer cell lines.

Introduction

Colorectal cancer (CRC) as a malignant cancer affecting both male and female, is ranked the third most common cancer worldwide and second most frequent cancer in Malaysia (GLOBOCAN 2020). Significant associations between dietary factors and CRC risk have been determined, in addition to smoking and alcohol intake (O'keefe, 2016). Regular consumption of fruits and vegetables was demonstrated effective in reducing CRC risk as polyphenolic compounds in plants contribute to decreasing cell adhesion process, migration, and tumour angiogenesis (Baena and Salinas, 2015). Standard chemotherapy regimens in treating CRC patients accommodates the use of cancer drug particularly 5-fluorouracil and doxorubicin hydrochloride that function by inhibiting DNA synthesis (Che and DeVita, 2015). Despite higher survival rate in patients, the adverse toxicity risk associated with these chemotherapy drugs need to be taken into account (Fotheringham et al, 2019). Therefore, the search for effective phytochemical compounds as antiproliferative agent continues.

Anthraquinone, an aromatic compound with a 9, 10-dioxoanthracene core can be found abundantly in several plants such as rhubarb root, aloe vera, morinda and senna leaf (Khan, 2019). It is reported to display pharmacological properties including anti-inflammatory, antioxidant, antimicrobial and anticancer (Duval et al., 2016). Zamakshshari et al. (2017) has reported that anthraquinone compounds obtained from *Morinda citrifolia* exhibited promising *in vitro* antitumor activity and selective against CRC cells. Following this, eight *Morinda citrifolia* isolated anthraquinone compounds were evaluated for cytotoxicity activity against CRC cell lines.

CRC is associated with a series of genetic alteration involving various pathway such as Wnt signalling pathway, Ras signaling pathway and p53 mediated apoptosis pathway. Being the crucial players of these pathway, β-catenin, p53 and KRAS genes are always found mutated in CRC, resulting in resistance to current therapies, conferring poor prognosis (Aran et al., 2016). Mologni et al. work in 2012 has reported promising combination therapeutic strategy in CRC by down regulating both β-catenin and KRAS simultaneously. Meanwhile, study by Hou et al. (2019) showed that the autoregulatory negative