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SHORT COMMUNICATION



Bixa orellana L. carotenoids: antiproliferative activity on human lung cancer, breast cancer, and cervical cancer cells *in vitro*

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ABSTRACT

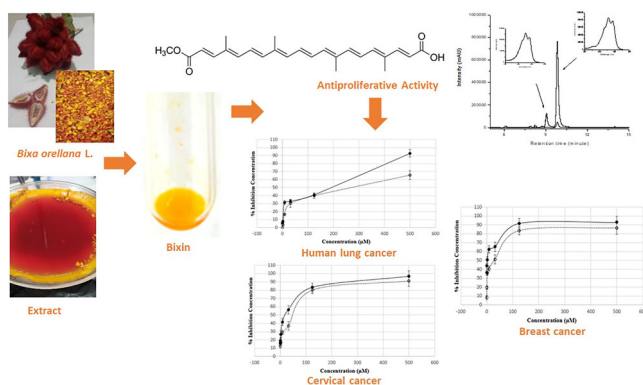
Emerging evidence on the potential pro-oxidant effect of carotenoids provokes apoptosis of cancer cells. *Bixa orellana* L. is native to Central and South America, interestingly, is also cultivated worldwide. Apo-carotenoids present in *B. orellana* L. are mainly dominated by bixin and norbixin and demonstrate fundamental antioxidant activity. Anti-proliferative activity on human cancer cells is rarely investigated. We isolated bixin from *B. orellana* L. found in the island of Java using Ultra-Fast Liquid Chromatography and confirmed the isolated compound using Liquid Chromatography-MS/MS. Bixin and crude extract were examined on human lung cancer (A549), cervical cancer (HeLa), and breast cancer (MCF-7). Anti-proliferative activity revealed to be promising on both, the isolated pigment and crude extract. Further investigation on the mechanism of action and effect on other cell lines, both *in vitro* and *in vivo*, are required before clinical translation.

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1. Introduction

Metabolic reaction in normal cells produces reactive oxygen species (ROS) by-products (Liguori et al. 2018). The intracellular antioxidant system scavenges ROS and prevents cellular damage. Antioxidant molecules, such those polyphenols, flavonoids, and member of carotenoids have been known for antioxidant effect and have furnished optimistic activity in a particular clinical setting (Wang et al. 2015; Song et al. 2017; Beydoun et al. 2019; Rattanavipanon et al. 2021). Diverse functional groups and isomer configuration of *cis*- (-Z) and *trans*- (-E) on the hydrocarbon backbone affect the bioactivity of carotenoids, in which the Z-isomers often demonstrate higher bioavailability and antioxidant activity, also often associated with thrilling pro-oxidant actions in lipid peroxidation (Shin et al. 2020). The bioactivity of carotenoids also depends on the concentration that can affect the presence of other carotenoids, oxygen, and new free radicals as observed in the study using MCF-7 breast cancer cells (Sowmya et al. 2017) and human leukemia HL-60 cells (Ganesan et al. 2011). Unlikely normal cells, cancer cells generate a higher amount of ROS due to the rapid metabolism of the cancerous cell, increased metabolism dysfunction, increased lipid peroxidation, and the failure of antioxidant enzymes (Liguori et al. 2018). Few studies have suggested the dual function of carotenoids as an antioxidant in normal cells and also pro-oxidant function induced apoptosis in cancer cells (Shin et al. 2020). Characteristics of cancer cells also determine the cytotoxicity activity of carotenoids, as seen in estrogen receptor (ER) negative MDA-MB-231 human breast cancer cells that are more susceptible to lycopene treatments than the ER-positive MCF-7 cells (Gloria et al. 2014). Understanding carotenoid's fate on the biology system, on how carotenoids turn pro-oxidant and antioxidant in specific types of cells and tissues, is warranted. One of the purposes is to optimize the anti-proliferative modulation on human cancer cells.

A well-known carotenoid producing species, *Bixa orellana* L., is a small shrubby tree native to Central and South America and used as traditional medicine (Giorgi et al. 2013). Between the 16th and 17th centuries, *B. orellana* L. was distributed to Southeast Asia, African, the Caribbean, and has since been cultivated in tropical regions including India, Srilanka, and Java (Ventosa 2018). Bixin constitutes 70–80% of all pigments present in *B. orellana* L. seed membrane while norbixin makes up the remaining 20% (Reith and Gielen 1971). These two pigments are also referred to as annatto and are traditionally used as natural food coloring (Bouvier et al. 2003; Raddatz-Mota et al. 2017) and cosmetic (Bouvier et al. 2003; Ntohogian et al. 2018). In the context of traditional medicine, some studies demonstrate broad pharmacological activities of *B. orellana* L. seeds, such as antioxidant activity, nephroprotective effect, and lipid-lowering effect (Kiokias and Gordon 2003; Paula et al. 2009; Rivera-Madrid et al. 2016; Souza et al. 2016; Roehrs et al. 2017).

Cancer chemopreventive compounds from natural products, including from the family of tocotrienols, is of interest due to the unique chemical structure resulting in broader pharmacological effect and reduced toxicity-induced side effects when compared to synthetic anticancer drugs (Marelli et al. 2019). Few studies on annatto exhibit selective antimyeloma activity (Tibodeau et al. 2010), induce apoptosis of human Hep3B hepatocellular carcinoma cells (Kumar et al. 2018), and tumor growth inhibition in HER-2/neu transgenic mice (Pierpaoli et al. 2013). Average daily intake of

annatto extract in North American and some Latin American countries is higher as compared to Acceptable Daily Intake (ADI) regulated by WHO and Committee of Food Additives (0–12 mg/kg body weight). No toxicity issue is found after administration of annatto by mammals at high levels (Hagiwara et al. 2003; Bautista et al. 2004). Potency of annatto as cancer chemopreventive effects is indeed promising. Cancer is a complex genetic disease. Extensive heterogeneity within patients' cancer cells has important implications on the type of treatment provided (Loeb et al. 2003). Thus, an in-depth investigation of annatto on various cell types of cancer is highly required, especially to measure its efficacy and ensure safe transition into the clinics.

We further investigated, for the first time, inhibition of cancer proliferation by annatto pigment and crude extract of *B. orellana* L. collected from Java (Figure S1) in three most prevalent cancer cell lines. Anti-proliferative effect and potency of pro-apoptosis was discussed to gain broader insight for further in-depth investigation.

2. Results and discussion

The average yield of seed extract was $3.73 \pm 0.33\%$. Kurniawati et al. (2007) confirmed that yield of annatto seed extract is 3.75% (Kurniawati et al. 2010). Samples from previous and current study were sourced from the same area. We extended our current study to isolate two main carotenoids, bixin, and norbixin. Acetone was used to dilute the carotenoid phase gathered from the fractionation. The diluted carotenoid was identified using UFLC in which Bixin was detected at retention time $t_R = 9.819$ min and norbixin at retention time $t_R = 9.046$ min (Figure S2). Isolated bixin from column chromatography has been confirmed using LC-MS/MS. Fragmented spectra at 450 nm indicates the presence of bixin, with fragmentation $377 [M + H - 18]^+$, $363 [M + H - 32]^+$, $335 [M + H - 32 - 28]^+$, $317 m/z$ (Figure S6-9), similar with available references (Chisté et al. 2011). Norbixin was not further identified as only low amounts were obtained.

The current study investigated the anti-proliferative activity of the crude extract and isolated bixin that had not been performed in the previous study. Antiproliferative assay shows profound results on three types of cells, especially HeLa and MCF-7, with the crude extract having greater activity than the isolate bixin (Figure S10a–c). IC_{50} of crude extract were 185.54 ± 14.46 , 17.90 ± 3.00 , and $2.06 \pm 0.30 \mu M$, while IC_{50} of isolated bixin were 259.38 ± 28.98 , 43.87 ± 3.06 , and $14.38 \pm 0.55 \mu M$ against A549, HeLa, and MCF-7 cells, respectively.

Cis-bixin has been identified to possess profound anti-myeloma effect (Tibodeau et al. 2010). *Cis-trans* isomerization of bixin was discovered in the early year of discovery (Zechmeister 1960). Bixin was confirmed as the apo-carotenoid 90-*cis*-bixin (methyl hydrogen 90-*cis*-6,60-diapocarotene-6,60-dioate, $C_{25}H_{30}O_4$), and commonly referred to as *cis*-bixin. *Cis*-bixin is normally soluble in most polar organic solvents showing an orange color (Scotter 2009). However, during exposure in solution, *cis*-bixin may be converted to the all-*trans* isomer due to its instability. *Trans*-bixin is the more stable isomer, has similar structure to the *cis*-isomer, but shows a red color in solution (Scotter 2009). During extraction and fractionation process, *cis*-bixin can possibly undergo isomerization, giving a mixture of all-*trans*- and *cis*-bixin in variable proportions and other degradation products, depend on the solvent used during extraction,

temperature, and time. The presence of *cis*-bixin in the extract form may prevent isomerization to all-*trans*-bixin, and thus possibly contribute to the greater activity than isolated bixin (Figure S10a–c).

A549 cells show reduced sensitivity to annatto seed extract and bixin when compared to other cell lines used in this study, HeLa and MCF-7 (Figure S10a–c). The reason underlying this reduced activity is most likely due to the mechanism of multidrug resistance reported in A549, including activation of efflux pump by drug transporter (Xu et al. 2014; Lin et al. 2020) and increased mitochondrial activity (Gao et al. 2019). Several clinical and pre-clinical studies support evidence that protein transporter plays a vital contribution to the multidrug resistance of cancer cells (Xiao et al. 2021), such as ABCC1 found in human small-cell lung cancer cell lines (Cole et al. 1992). The resistance of lung cancer A549 to crude extract and isolated bixin may be due to carotenoids acting as the substrate of drug transporter, which is overexpressed in the A549 cells. Carotenoids, as a substrate, bind to the transporter (Tinoush et al. 2020). However, without sufficient concentration, carotenoids were not able to enter cancer cells and interfere with intracellular processes, and thus resulting in failure to inhibit growth and/or promote apoptosis.

Likely, it has been shown against hepatocellular carcinoma (Kumar et al. 2018), myeloma cells (Tibodeau et al. 2010), melanoma cells (Anantharaman et al. 2016; de Oliveira Júnior et al. 2019), and human leukemia cell (Santos et al. 2016). One proposed mechanism underlying this activity is via ROS-mediated apoptosis (Tibodeau et al. 2010; Anantharaman et al. 2016; Santos et al. 2016; de Oliveira Júnior et al. 2019). Carotenoids are a popular antioxidant agent with the ability to modulate the intracellular redox status, exerting both antioxidant and pro-oxidant properties, depending on concentration, cell types, and microenvironment of the cells (Sznarkowska et al. 2017). Besides the modulation on drug transporter, the mechanism underlying the unfavorable interaction between annatto seed extract and isolated bixin in A549 cells can also be due to the redox status, in which modulation of natural antioxidant activity was more significant than the capacity as pro-oxidant induced apoptosis.

3. Experimental

Provided in [Supplementary File](#)

4. Conclusions

Annatto seed extract performed profound anti-proliferative activity when compared to isolated bixin in three types of human cancer cell lines. Stable form of *cis*-bixin in the extract, along with the combination norbixin and other carotenoids, may exert more potent activity instead of the single isolated bixin. Redox signaling pathway-induced apoptosis and modulation on drug transporter requires further in-depth investigation on a specific type of cancer and tumor. It may generate rational cancer prevention and therapy including its combination with other conventional chemotherapeutic drugs.

Disclosure statement

Authors declare no conflict of interest.

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