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Sorayya Ghasemi, Zahra Lorigooini, JokoPriyanto Wibowo & Hossein Amini-khoei

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SHORT COMMUNICATION

Tricin isolated from *Allium atrovioleaceum* potentiated the effect of docetaxel on PC3 cell proliferation: role of miR-21

Sorayya Ghasemi^a, Zahra Lorigooini^b, JokoPriyanto Wibowo^{c,d} and Hossein Amini-khoei^b

^aCellular and Molecular Research Center, Basic Health Sciences Institute, Shahrekord University of Medical Sciences, Shahrekord, Iran; ^bMedicinal Plants Research Center, Basic Health Sciences Institute, Shahrekord University of Medical Sciences, Shahrekord, Iran; ^cChemical and Pharmaceutical Biology Department, Groningen Research Institute of Pharmacy, University of Groningen, Groningen, The Netherlands; ^dFaculty of Pharmacy, University of Muhammadiyah Banjarmasin, Banjarmasin, Indonesia

ABSTRACT

For more effectiveness and overcoming the drug resistance Chemotherapy agents, the combination treatment is raised. Flavonoids with different anti-cancer effects are an appropriate choice as lead compounds. Over expressed MiR-21 in prostate cancer is associated with metastasis and drug resistance to chemotherapy with Docetaxel. In this study, the anticancer effect of 4', 5, 7-Trihydroxy-3', 5'-dimethoxyflavone (Tricin) was investigated with Docetaxel on PC3 cell line. Tricin was initially isolated from the *Allium atrovioleaceum* by column chromatography and recrystallization method. The chemical structure of isolate was elucidated by spectroscopic techniques. IC₅₀ of Tricin and Docetaxel were assessed 117.5 ± 4.4 µM and 0.1 ± 0.02 nM by MTT assay, respectively. Analysis of results indicates the synergistic effect of combination therapy on decreased proliferation. MiR-21 in treated cells with Tricin significantly decreased compared to control cells. So, Tricin can be effective in the reduction of metastasis and drug resistance of Docetaxel.

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CONTACT Zahra Lorigooini ✉ Zahralorigooini@gmail.com, gueini.z@skums.ac.ir

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1. Introduction

Prostate Cancer (PCa) is a drug resistance cancer. For overcoming the drug resistance, the combination drug treatments are suggested. The main benefit of combination therapy is to avoid side effects through a drug synergism (Batra and Sharma 2013). Docetaxel (DOC) and is widely used in PCa chemotherapy. Recurrence in PCa is observed due to resistance to chemotherapy drugs (Freedland et al. 2007). The manipulation of associated miRNAs with cancers could be used as an anti-cancer instrument in the future (Ghasemi et al. 2015). MiR-21 with various roles in drug resistance is over expressed in cancers including PCa (Papagiannakopoulos et al. 2008). Many derived natural compounds such as Flavonoids have been approved by the FDA as chemotherapeutic agents. Anti-cancer effects of flavonoids depend on factors such as chemical structure and the source of cancer (Harborne 2013). *Allium* genus such as *Allium atrovioleaceum* are a rich source of compounds that have been consumed as medicine and food for many years (Lee et al. 2015). Tricin as a flavone is 4', 5, 7-Trihydroxy-3', 5'-dimethoxyflavone with different biological effects such as antioxidant, anti-influenza virus and a protective agent in liver function (Moheb et al. 2013). In this study, for the first time, the anti-proliferation effect of isolated Tricin from *A. atrovioleaceum* was examined on PC3 cell line in combination with Doc. In order to evaluate the effect of this natural compound on the expression of miR-21 as a known resistance to Doc, in PC3 was measured.

2. Results and discussion

The MeOH extract of Aerial parts of *A. atrovioleaceum* partitioned between ethyl acetate (EtOAc) to yield an EtOAc-soluble fraction. The EtOAc fraction was chromatography by silica gel. The g obtained subfraction was purified by Sephadex LH-20 and further recrystallized to afford compound I (yield: 0.11%). Compound I was analyzed by MS: 330 *m/z* and it corresponded to the molecular formula $C_{17}H_{14}O_7$. The 1H -NMR spectrum showed characteristic signals of flavonoid class, which are singlet at the δ_H 7.325 corresponding to hydrogens H-2' and H-6' of ring B and two doublets at δ_H 6.574 ($J = 2.0$ Hz) and δ_H 6.218 ($J = 2.0$ Hz) corresponding to hydrogens H-8 and H-6 of ring A, respectively, and a singlet at δ_H 6.979 referred to H-3. The ^{13}C -NMR spectrum presented signals at δ_C 103.5 and 164.2 which are typical carbons of C-3 and C-2 of flavone aglycone, moreover, a signal at δ_C 181.7 is characteristic of the carbonyl of ring C. The ^{13}C -NMR spectrum also showed signals at δ_C 157.3, 98.8, 163.6, 94.2, 161.4, 103.6 referred to carbons C-5, C-6, C-7, C-8, C-9 and C-10 of ring A, respectively, and signals at δ_C 120.3, 104.3, 148.2, 139.8 correspond to C-1', C-2' and C-6', C-3' and C-5', C-4' of ring B. This compound was confirmed as Tricin (supplementary data Figures S4–S10). Its identity was confirmed by comparison of its spectroscopic data with the published data for the compound. It is worth mentioning that this compound was previously isolated from the family Poaceae and Palmaceae yield (Jiao et al. 2007; Liu et al. 2012; Moheb et al. 2013), but this is the first report of its isolation from Alliaceae. Results indicate that *A. atrovioleaceum* might be the rich source for isolation Tricin.

Various concentrations of Doc and Tricin were added to 5000 PC3 cells in per 96-well plates. Concentration range which firstly shows the cytotoxic effects of Tricin for this natural compound in this study is also suggested for future studies with this compound. Tricin anti-cancer effect was analyzed for the first time through the impact on the reduction of

proliferation individually and in combination with a chemotherapy drug (DOC) by MTT assay. MTT assay showed a reduction after treatment with various concentrations of DOC (nM) as well as tricin (μM) (dose-response anti-proliferative effects for 48 h). As shown in supplemental data Figures S1A and S1B, IC_{50} Tricin was $117.5 \pm 4.4 \mu\text{M}$. IC_{50} of Doc was 0.1 ± 0.02 nM. The Compusin software to determine CI also showed that the combination of these two compounds has a significant depressing effect on cell viability. The number of survival treated cells was reduced by increasing the concentration of Tricin compared to control. In diagram Fa–CI, areas of the curve Fa which are below dots CI ($\text{CI} < 1$) indicate synergism, $\text{CI} = 1$ indicates (Additive) effects of drugs and $\text{CI} > 1$ or putting the top of line CI indicates the existence of antagonism between drugs. Curves Fa–CI and Fa–DRI were drawn based on the value Fa by the Compusin software (supplemental data Figure S2). As the results in curves show, the synergistic effect ($\text{CI} < 1$) can be seen in all values of Fa, but 0.1 and on the other hand, the desirable dose reduction ($\text{DRI} > 1$) was seen for all Fa but 0.1 of Tricin. In this study, the concurrent effect of DOC along with Tricin on PC3 cell line, which is partly resistant to the chemotherapy drug (Takeda et al. 2007) was investigated. The simultaneous effectiveness method was selected as the best mode for the effectiveness of the drugs. The greatest synergistic effect was observed in concentration (0.01 nM) of DOC and concentration (60.0 μM) of Tricin. By combining these two concentrations, ($\text{CI} = 0.37$) was obtained (supplemental data Figure S2). The mechanism and molecular pathway of the effectiveness of this herbal medicine require more investigations. Real-Time PCR was used for quantification of miR-21 on a Real-Time rotary analyzer (Rotor-Gene 3000). RNAU6B was used as an internal control. miR-21 expression confirmed that with Tricin, 48 h after treatment with 120 and 140 μM concentrations, the miR-21 expression fold change was 0.69 and 0.65 So, miR-21 expression level significantly ($p < 0.05$) decreased (Figure S3). Epigallocatechin-3-gallate inhibits as an androgen receptor signalling through miR-21. (Siddiqui et al. 2011). Today, PCa treatments have been designed by targeting miR-21. So if a drug with fewer sides reduces the expression levels of miR-21, it will certainly be effective. MiR-21 was overexpressed in men with resistance to DOC and metastasis (Papagiannakopoulos et al. 2008). PC3 cell line is resistant to hormone and metastasis line. It was shown for the first time that Tricin could decrease expression level of miR-21. Therefore, it can be hoped to aid measures in the treatment with more research on safety and complementary treatments like natural medicines such as flavonoids like Tricin by targeting miR-21.

3. Conclusion

Hence, it is suggested that Tricin, as a natural therapy, be entered into *in vivo* studies. If the results are acceptable, it could be used as a natural complementary therapy in the future.

Supplementary material

Supplementary Figures S1–S10 relating to this article are available online.

Disclosure statement

No potential conflict of interest was reported by the authors.

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ORCID

JokoPriyanto Wibowo <http://orcid.org/0000-0003-4080-3724>

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