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**SDI Review Form 1.6**

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| Journal Name: | Asian Hematology Research Journal |
| Manuscript Number: | **Ms_AHRJ_53095** |
| Title of the Manuscript: | **HOP-DERIVED XANTHOHUMOL INDUCES HL-60 LEUKEMIA CELLS DEATH** |
| Type of the Article | **Original Research Article** |

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**PART 1: Review Comments**

| | **Reviewer's comment** | **Author's comment** *(if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)* |
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| **Compulsory** REVISION comments | **Title**<br>**HOP-DERIVED XANTHOHUMOL INDUCES HL-60 LEUKEMIA CELLS DEATH**<br>Suggested Title: **XANTHOHUMOL INDUCES HL-60 LEUKEMIA CELLS DEATH**<br>*Comment*: xanthohumol was commercially obtained and not purified from the plant *Humulus lupulus* in the manuscript; please, explain in *Materials and Methods*.<br><br>**Abstract**<br>*Comments*: please, improve the item.<br><br>**Background.** Acute promyelocytic leukemia (APL) affects both kids and adults, however it is more prevalent in younger population. Although APL has a favorable prognostic, patients that do relapse (what?) often do not favorable respond to additional chemotherapy. Therefore, there is a need to further identify ways to overcome these challenges.<br>**Hypothesis:** In this study, we examined antileukemic effects of xanthohumol, a prenylated flavonoid derived from hops (*Humulus lupulus*), on human promyelocytic HL-60 cells.<br>**Materials and Methods.** HL-60 cells were exposed to different concentrations of xanthohumol (μM) for 24 h. Cell viability, cell morphology, chromatin condensation, cPARP-1 level, and caspase-3 activation, and the expression of p21WAF1/Cip1 were analyzed.<br>**Results.** Xanthohumol reduced HL-60 cell viability in a dose-dependent manner. Xanthohumol induced a dose-dependent ~~profound~~ morphological changes including cell shrinkage and blebbing, and significantly increased the number of cells with condensed chromatin. Xanthohumol significantly increased the level of cPARP-1, active caspase-3, and the expression of p21WAF/CIP mRNA.<br>**Conclusion.** These data indicate that xanthohumol induces HL-60 cells death by regulating cell cycle progression and apoptosis. This study suggests that xanthohumol may have antileukemic preventive effects.<br><br>**Key words**: Acute promyelocytic leukemia, apoptosis, caspase-3, p21, xanthohumol, plant derived, HL-60 cells<br><br>Suggested **Key words**: xanthohumol, acute promyelocytic leukemia, HL-60 cells, apoptosis, caspase-3, p21.<br><br>**Abbreviations**<br>*Comments*: please, adjust item and add not mentioned abbreviations.<br><br>APL acute premyelocytic promyelocytic leukemia<br>PARP-1 polymerase associated reactive protein 1<br>cPARP-1 cleaved PARP-1<br>FBS Fetal Bovine Serum<br>XN xanthohumol<br><br>**Introduction**<br>*Comments*: please, improve item and use abbreviations. Figure 1 is not new, and then it is not necessary. Please explain clearly in the text "the disease relapses, the mortality rate is high".<br><br>Acute promyelocytic leukemia (APL) a subtype of acute myeloid leukemia (AML) represents 5-20% of AML. Each year ~ 600-800 new cases of leukemia are diagnosed in | |

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| | the USA [1]. Although APL has a good prognosis, if untreated or if the disease relapses, the mortality rate is high [2]. Approximately, 30% of patients relapse [3]. Epidemiologic studies show that APL is more common in children and young adult patients and among Hispanics [4]. Although new therapeutic approaches have been developed, APL still remains an aggressive subtype of AML and with high rates of early death [5-6]. Indeed, approximately 17.3% of cases<br>undergo early death within one month of diagnosis due to severe hemorrhages [7]. Therefore, finding new approaches to improve APL treatment outcome is of great importance. Plant-based compounds alone or in combination with chemodrugs have been shown to have antitumor effects and to improve treatment outcome of several malignant hematologies including Hodgkin's disease and acute lymphoblastic leukemia [8-11]. For example, plant-derived alkaloids vincristine and vinblastine are approved for the treatment of hematological malignancies and other cancers [10-11]. Vincristine is used to treat childhood leukemia whereas vinblastine is used<br>in combination with chemodrugs to treat breast and bladder cancers [12-14]. Although vincristine is successful for childhood leukemia often leads to neuropathy 14-15]. Thus identifying plant compounds with antileukimic properties and less toxicity will contribute to improve treatment outcome [11, 16-17]). Plant-derived prenylated flavonoid, xanthohumol (XN), has been shown to have biological properties. Xanthohumol is present in the cones of hop plant (*Humulus lupulus* L.) Fig. 1 [18].<br>~~**Figure 1**. Hop plant cone (Humulus lupulus L) (A), and xanthohumol chemical structure (B).~~<br>Xanthohumol is a prenylated chalcone found in the cone of hop plant [18].<br>In hops, xanthohumol content vary from 0.1% to 1% dry weight [19]. In addition of being used in brewing industry, numerous studies also showed xanthohumol's numerous biological effects including anti-inflammatory, anti-oxidant, and anti-infectious [20-23]. Recent studies showed xanthohumol increased lipid and glucose metabolism [24-26]. Xanthohumol anticarcinogenic<br>properties have been shown on many different cancer cell types including liver, prostate, endometrial, colon, and lung [26-31]. The exact mechanism by which xanthohumol exerts its effects is not fully understood, however studies suggest that it inhibits cell proliferation and induces apoptosis by upregulating p53 and inducing S phase cell cycle control genes [31-32].<br>While xanthohumol anti-carcinogenic effects were studied on many cancer cell types, fewer studies examined xanthohumol effects on human acute promyelocytic leukemia. In the present study, we examined xanthohumol effects on acute promyelocytic leukemia HL-60 cells.<br><br>**RESULTS**<br>*Comments*: Please, explain with clear legends all Figures.<br><br>**REFERENCES**<br>*Comment*: Please revise item; some references mention doi/DOI, some journals are abbreviated, others no. From 49 references 31 are above 2009. | |
| **Minor** REVISION comments | | |
| **Optional/General** comments | **General Comments**<br>Please revise the English language of manuscript, in general, and according to *Comments*. Use abbreviations since they were established. | |

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**PART 2:**

| | **Reviewer's comment** | **Author's comment** *(if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)* |
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| **Are there ethical issues in this manuscript?** | *(If yes, Kindly please write down the ethical issues here in details)* | |

As per the guideline of editorial office we have followed VANCOUVER reference style for our paper.

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