**UNIVERSITI PUTRA MALAYSIA**

# *PROTECTIVE PROPERTIES OF STINGLESS BEE HONEY IN ZEBRAFISH EMBRYO EXPOSED TO GAMMA IRRADIATION*

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By

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Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Master of Science

January 2021

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Master of Science

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**Chair : Professor Latifah binti Saiful Yazan, PhD**
**Institute : Bioscience**

There are many benefits of ionizing radiation applications particularly in the field of medicine, industry, agriculture and research. As the use increases, the risk of getting health hazards is the major concern if not properly used or contained. Overexposure to ionizing radiation can cause acute health effects or late consequences which is cancer risk. At the cellular level, the radiation will induce DNA damage and after that apoptosis as leading route of cell inactivation. Cells exposed to ionizing radiation can release signals that induce very similar effects in non-targeted neighbouring cells, a phenomenon known as bystander effects. In this study, we have used the zebrafish as the powerful *in vivo* model organism to evaluate the potential of Kelulut honey (KH) in reducing the harmful effects of gamma irradiation. Several types of honey are well documented to reduce radiation-induced damage *in vitro* and *in vivo*. All of the honey were chosen based on antioxidant properties reported in previous studies. None of the studies have discussed on the potential of KH as radioprotectant. Our aim was to investigate the effectiveness of KH in radioprotecting the zebrafish embryo from adverse effects of gamma radiation. Zebrafish embryos were collected according standard guidelines. Briefly, 24 hours post fertilization (hpf) zebrafish embryos were irradiated at the doses of 11 – 20 Gy of gamma ray (caesium-137). The embryos were examined for lethality and abnormalities until 96 hours post-irradiation (120 hours post fertilization). The optimum concentration of KH for zebrafish embryos treatment was obtained through toxicity evaluation. Evaluation of KH for radioprotective properties has been performed by using phenotypic assay and immunohistochemistry analysis involving γH2AX and caspase-3 proteins represented DNA damage and apoptosis. All of the results were were analyzed using two-way ANOVA followed by Tukey post hoc test using GraphPad Prism version 8 and presented as mean ± SEM. Amifostine was used as a positive control for comparison purposes. The dose of KH selected for determination of survival, morphology, DNA damage and apoptosis was 8 mg/mL. KH also was found to be not toxic in the zebrafish embryos depending on the concentration used. For lethality evaluation, coagulated zebrafish embryos found at 24 and 48 hours post-irradiation. The highest coagulation were from 19 and 20 Gy of the irradiation and the lowest at 11 Gy. LC50 value of gamma radiation at 120 hpf was 13.68 Gy. Several combinations of abnormality (body curvature, microphthalmia, microcephaly and pericardial oedema) were found in the study. KH treatment was found to increase survival rate up to 20 Gy ($p<0.05$). It is also found to reduce morphological abnormalities of embryos specifically body curvature incidence. Bystander embryos pre-treated with KH and amifostine were found to reduce lethality and abnormality effect of irradiated-embryo conditioned media (IECM) irradiated. The lethality and abnormality occurrence in the study overall were independent of irradiation doses. Amifostine was identified to reduce DNA damage in the zebrafish embryos at 11 to 20 Gy of gamma irradiation ($p<0.05$). KH treatment was recorded to be significantly reduced the DNA damage at 14 and 15 Gy of radiation exposure ($p<0.05$). The DNA damage was only recorded in the bystander zebrafish embryos at 18 and 19 Gy of IECM exposure ($p<0.05$). Amifostine showed less protective effect to reduce DNA damage at 18 and 19 Gy and KH did not reduce the intensity of γH2AX in the bystander embryos. Similar to DNA damage analysis, amifostine was found to reduce the apoptosis incidence in the zebrafish embryos at 11 to 20 Gy ($p<0.05$). KH was recorded to reduce the apoptosis at 11, 12, 13 and 15 Gy of the irradiation dose ($p<0.05$). Caspase-3 intensity was found to be similar at 11 to 18 Gy in all of the bystander embryos which was no apoptosis incidence showed in the analysis. Amifostine was identified to reduce the apoptosis at 20 Gy of IECM exposure and KH was not reduce the apoptosis incidence in the bystander embryos ($p<0.05$). The collective results suggest that KH exhibited radioprotective properties in zebrafish embryos by reducing the adverse effects of gamma irradiation and can be categorized as the one of potential Type A2 radioprotectant which focused to scavange free radicals by ionizing radiation in the study. Besides, KH can be developed as a future radioprotector.

Keywords: Kelulut honey, radioprotective agent, zebrafish model, bystander effects

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia
sebagai memenuhi keperluan untuk Ijazah Master Sains

# SIFAT PERLINDUNGAN MADU LEBAH KELULUT DALAM EMBRIO ZEBRAFISH YANG DIDEDAHKAN PADA SINARAN GAMA

Oleh

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Sinaran radiasi mempunyai banyak kegunaan yang bermanfaat terutamanya dalam bidang perubatan, industri, pertanian dan penyelidikan. Ketika penggunaannya meningkat, risiko mendapat bahaya kesihatan menjadi perhatian utama jika tidak digunakan atau dibendung dengan betul. Dedahan terhadap sinaran mengion yang melampau boleh menyebabkan kesan kesihatan akut atau kesan yang lewat iaitu risiko kanser. Pada peringkat sel, radiasi akan menyebabkan kerosakan DNA dan kemudiannya apoptosis sebagai laluan utama kepada inaktivasi sel. Sel yang terdedah kepada sinaran pengion dapat melepaskan isyarat yang menimbulkan kesan yang serupa pada sel yang tidak disinarkan atau lebih dikenali sebagai fenomena kesan bystander. Dalam kajian ini, kami telah menggunakan zebrafish sebagai model organisma *in vivo* yang kuat untuk menilai potensi madu Kelulut (KH) dalam mengurangkan kesan berbahaya penyinaran gamma. Beberapa jenis madu telah didokumentasikan dengan baik untuk mengurangkan kerosakan akibat sinaran secara *in vitro* dan *in vivo*. Semua madu dipilih berdasarkan sifat antioksidan yang dilaporkan dalam kajian sebelumnya. Tidak ada kajian yang membincangkan potensi KH sebagai pelindung sinaran. Tujuan kami adalah untuk mengkaji keberkesanan KH dalam melindungi embrio zebrafish dari kesan buruk sinaran gama. Embrio zebrafish dikumpulkan mengikut garis panduan piawai. Secara ringkas, embrio zebrafish pada 24 jam selepas persenyawaan (hpf) disinari pada dos sinar gama 11 - 20 Gy (cesium-137). Embrio – embrio telah diperiksa kematian dan keabnormalan sehingga 96 jam selepas penyinaran (120 jam selepas persenyawaan). Kepekatan optimum KH untuk rawatan embrio zebrafish diperoleh melalui penilaian ketoksikan. Penilaian KH untuk sifat radioprotektif telah dilakukan dengan menggunakan analisis fenotipik dan analisis imunohistokimia yang melibatkan protein γH2AX dan caspase-3 yang mewakili kerosakan DNA dan apoptosis. Semua keputusan yang diperoleh telah dianalisis dengan ANOVA dua hala diikuti oleh ujian post hoc Tukey dengan menggunakan GraphPad Prism versi 8. Amifostine telah digunakan sebagai kawalan positif untuk tujuan perbandingan. Dos KH yang dipilih untuk menentukan kelangsungan hidup, morfologi, kerosakan DNA dan apoptosis adalah 8 mg/mL. KH juga didapati tidak toksik pada embrio zebra bergantung pada kepekatan yang digunakan. Untuk penilaian kematian, embrio zebrafish yang terkoagulasi ditemui pada 24 dan 48 jam selepas penyinaran. Koagulasi tertinggi adalah dari penyinaran 19 dan 20 Gy dan terendah adalah pada 11 Gy. Nilai LC50 radiasi gamma pada 120 hpf adalah 13.68 Gy. Beberapa gabungan kelainan (kelengkungan badan, mikrofthalmia, mikrosefali dan edema perikardial) ditemui dalam kajian ini. Rawatan KH didapati meningkatkan kadar kelangsungan hidup hingga 20 Gy ($p<0.05$). Ia juga didapati dapat mengurangkan keabnormalan morfologi embrio khususnya kejadian kelengkungan badan. Embrio bystander yang dirawat dengan KH dan amifostine didapati dapat mengurangkan kesan kematian dan keabnormalan daripada media kondisi embrio (IECM) yang disinari. Kematian dan kejadian abnormaliti dalam keseluruhan kajian tidak bergantung pada dos penyinaran. Amifostine dikenal pasti dapat mengurangkan kerosakan DNA pada embrio zebrafish pada 11 hingga 20 Gy penyinaran gamma ($p<0.05$). Rawatan KH dicatat dapat mengurangkan kerosakan DNA secara signifikan pada pendedahan radiasi pada 14 dan 15 Gy ($p<0.05$). Kerosakan DNA hanya dicatat pada embrio zebrafish bystander pada pendedahan IECM 18 dan 19 Gy ($p <0.05$). Amifostine menunjukkan kesan radioprotektif yang kurang bagi mengurangkan kerosakan DNA pada 18 dan 19 Gy dan KH tidak mengurangkan intensiti γH2AX pada embrio bystander. Seiring dengan analisis kerosakan DNA, amifostine didapati dapat mengurangkan kejadian apoptosis pada embrio zebra pada 11 hingga 20 Gy ($p<0.05$). KH direkodkan untuk mengurangkan apoptosis pada 11, 12, 13 dan 15 Gy dari dos penyinaran ($p<0.05$). Intensiti caspase-3 didapati serupa pada 11 hingga 18 Gy di semua embrio bystander iaitu tiada kesan apoptosis dilihat daripada analisis. Amifostine dikenal pasti mengurangkan apoptosis pada 20 Gy pendedahan IECM dan KH tidak mengurangkan kejadian apoptosis pada embrio bystander ($p<0.05$). Keputusan secara keseluruhannya menunjukkan bahawa KH memperlihatkan sifat radioprotektif pada embrio zebra dengan mengurangkan kesan buruk penyinaran gamma dan dapat dikategorikan sebagai salah satu radioprotektan Jenis A2 yang berpotensi untuk menumpaskan radikal bebas oleh sinaran pengion dalam kajian. Selain itu, KH dapat dikembangkan sebagai pelindung sinaran pada masa hadapan.

Kata kunci: Madu Kelulut, agent radioprotektif, model zebrafish, kesan bystander

# ACKNOWLEDGEMENTS

First and foremost, praise be to Almighty Allah for all his blessings for giving me patience and good health throughout the duration of this Master of Science research.

I am very fortunate to have Professor Dr. Latifah Saiful Yazan as a research supervisor. Thank you and appreciation to her whose insight and knowledge into the subject matter steered me through this research. Also, I would like to express my high appreciation to my co-supervisor Dr. Nur Fariesha Md Hashim and Dr. Annie Christianus.

Moreover, I am grateful to Mr. Shuhaimi Shamsudin, operator of Gamma Cell BIOBEAM Facility, Malaysian Nuclear Agency for the guidance throughout the irradiation process.

I would like to say a special thanks to Dr. Suzita Mohd Noor from Faculty of Medicine, Universiti Malaya, for sharing her knowledge in zebrafish research.

I am also thankful to all of my colleagues who are also Associate Professor Dr Latifah Saiful Yazan's students for all the considerate guidance.

I would like to express my sincere gratitude to Universiti Putra Malaysia Grant programme under project code GP-IPS/2018/9614700, funded by the Universiti Putra Malaysia.

Last but not least, to my dearest wife, Puan Nur Faizana Che Amram, my beloved mother, Puan Laila Mohd Sharif, my beloved father, Mr. Adenan Ayob, biggest thanks to them for all the support they have shown me through this research.

I certify that a Thesis Examination Committee has met on (date of viva voce) to conduct the final examination of (student's name) on his (her) thesis entitled ("Title of Thesis") in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the (insert the name of relevant degree).

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| | |
|---|---|
| KH | Kelulut honey |
| LC10 | Concentration at which 10% of lethality was observed |
| LC50 | Concentration at which 50% of lethality was observed |
| IECM | Irradiated-embryo conditioned media |
| TENORM | Technologically enhanced naturally occurring radioactive materials |
| ARS | Acute radiation syndrome |
| OH. | Hyrdroxyl |
| DSB | Double strand breaks |
| LET | Linear energy transfer |
| TNFR | Tumor necrosis factor receptor |
| DD | Death domain |
| FADD | Fas-associated death domain |
| ROS | Reactive oxygen species |
| GJIC | Gap-junctional intercellular communication |
| ATM | Ataxia-telangiectasia mutated |
| SOD | Superoxide dismutase |
| TLR5 | Toll-like receptor 5 |
| ACF | Aberrant crypt foci |
| PMNs | Polymorphonuclear neutrophils |
| RT | Radiotherapy |
| EAC | Esophageal adenocarcinoma |
| IACUC | Institutional Animal Care and Use Committee |
| OECD | Organisation for Economic Cooperation and Development |

| | |
|---|---|
| MNA | Malaysian Nuclear Agency |
| MAC | Maximum allowable concentration |
| IHC | Immunohistochemistry |
| PFA | Paraformaldehyde |
| BO | Body curvature with pericardial oedema |
| BC | Body curvature |
| MO | Microphthalmia with pericardial oedema |
| BOO | Body curvature with microphthalmia and pericardial oedema |
| BCO | Body curvature with microcephaly and pericardial oedema |
| AA | All abnormalities |
| IN | The irradiated zebrafish embryos group without any treatment |
| BNT | The untreated bystander embryos group |
| IKH | The irradiated embryos group pre-treated with KH |
| BKH | The bystander embryos group pre-treated with KH |
| IA | The irradiated embryos group pre-treated with amifostine |
| BA | The bystander embryos group pre-treated with amifostine |
| M | Microphthalmia |
| BM | Body curvature with microphthalmia |
| BMC | Body curvature with microphthalmia and microcephaly |
| MCO | Microphthalmia with microcephaly and pericardial oedema |
| MC | Microphthalmia and microcephaly |
| AUTS2 | Activator of transcription and developmental regulator |
| CNS | Central nervous system |
| RIBE | Radiation induced bystander effects |
| LCL | Lymphoblastoid cell line |

| | |
|---|---|
| IAP | Inhibitor of apoptosis |
| TGFβ | Transforming growth factor |
| TNFα | Tumour necrosis factor |
| TRAIL | TNF-related apoptosis-inducing ligand |

# CHAPTER 1

# INTRODUCTION

## 1.1. Background of Research

Radiation is an energy that comes from a variety of natural and artificial sources and may be able to penetrate various materials. It is travelling as waves or particles in environment. It can be divided into two types namely ionizing radiation and non-ionizing radiation. Ionizing radiation has sufficient energy to change the chemical composition of matter while non-ionizing radiation has less energy but still can elicit molecules and atoms causing them to vibrate faster. Ionizing radiation is emitted from radioactive atomic structures as high energy electromagnetic waves (gamma and x-rays) or actual particles, which are alpha, beta and neutrons (Goldman, 1982). Non-ionizing radiation derives from extremely low frequency (ELF), very low frequency (VLF), radio waves, microwaves, infrared radiation and visible light (Syaza et al., 2018).

Radiation has many beneficial uses in human life and its application is increasing recently. In medicine, radioisotopes are used extensively in diagnosis and therapy for a number of diseases. For diagnosis, x-rays can provide images to identify abnormal changes in body and tissues. The radioactive isotopes from gamma-rays sources can be used in cancer treatments by destroying the abnormal formed of cells. The industrial application of radiation is power generation based on the release fission energy of uranium. Other applications are the use of radioisotopes with high penetrating capability to capture defects image in welds and metal castings as well as to measure thickness of electroplates and to eliminate static charges in industries. Radioisotopes are employed in agricultural field as tracers. Selected fertilizers labelled with radioisotopes is important to find out the amount of fertilizer uptake by plants and the amount that is lost during the plant physiological processes (Singh et al., 2013).

Application of radiation have resulted in increasing number of human exposed to the risk of using it. Radiation workers may have higher risk to face radiation accidents. About 417 radiation accidents happened in year 1944 to 2000 and led to significant overexposure of at least one person (Turai and Veress, 2001). Exposure to high levels of radiations can cause acute health effects such as skin burns and acute radiation syndrome. Exposure to low levels of radiation does not cause immediate health effects, but contributes to cancer risk (Mraz and Becker, 2017). For cancer patients under radiotherapy treatment, radiation does not only kill the cancer cells but also causes side effects to neighbouring normal cells. Therefore, studies are needed to find a suitable and more effective radiation protection agent that has capability to reduce the harmful effects of radiation as well as protecting neighbouring non-irradiated cells.

Ionizing radiation can trigger the formation of free radicals, which induces biological damage even at a very low dose (Prasad, 2005). It can also cause DNA damage in the cells. Following the induction of DNA damage, a leading route of cell inactivation is apoptosis (Roos and Kaina, 2006). Apoptosis is a secondary response to DNA damage in order to protect a multicellular organism against a damaged cell (Wang, 2001). Ionizing radiation exposure often triggers the onset of p53-dependent apoptotic pathways or known as intrinsic apoptotic pathways (Liu et al., 2014). This involves other proteins activation such as puma, bax, cytochrome C, Apaf-1, caspase-9 and caspase-3. Although ionizing radiation effects have been well defined in a variety of *in vitro* models, the mechanisms as well as the presence of such effect *in vivo* is not well described (Chai and Hei, 2008). Therefore, the use of a suitable model organism is required for any radiobiological studies in order to develop more efficient and effective strategies to prevent, cure and reduce radiation harmful effects.

Amifostine is a known radioprotectant developed by Amifostine Walter Reed Army Institute to protect personnel from radiation sickness (Hall, 1985). It has capability to protect cells from damage by scavenging free radicals, was later assessed for a potential role in reducing the toxicities from radiation and chemotherapeutic agents. Besides, preclinical studies demonstrated that amifostine can selectively protect almost all normal tissues from the cytotoxic effects of some chemotherapeutic agents and radiation therapy (Kouvaris et al., 2007). However, clinical application of amifostine is currently limited due to its harmful side effects, including nausea and vomiting (Pandit et al., 2015). Therefore, there is a need to develop an effective as well as non-toxic radioprotectant agent. Natural products are non-toxic with proven therapeutic benefits and have been screened for their radioprotective potential in various *in vitro* and *in vivo* studies (Kuruba and Gollapalli, 2018). The use of natural products and dietary modulators in combination with radiation enhanced radioprotecting activities as well as protection of normal cells against radiation (Jagetia, 2007).

Honey is one of the natural products that has a potential to reduce harmful effects of ionizing radiation exposure and appropriate to be developed as radioprotectant agent. Previously, Tengku Ahmad et al. (2013) have tested Gelam honey against human diploid fibroblasts before gamma irradiation exposure. They found that the Gelam honey upregulated antioxidant enzyme to detoxify free radicals produced by ionizing radiation. On the other hand, a study on the effect of honey on radiation-induced oral mucositis in head and neck cancer patients was performed by Amanat et al. (2017). The results showed that Ziziphus honey significantly reduced the severity of muscositis in head and neck cancer patients under radiotherapy treatment. A study by Ahmad et al. (2012) identified that Tualang honey protected keratinocytes from adverse effects of ultraviolet radiation. In fact, the Tualang honey has the capability to reduce inflammation and DNA damage by radiation.

There were several types of honey have been used to test the the radioprotective effects against ionizing radiation. Basically, these honeys were chosen based on antioxidant properties reported in previous studies (Tengku Ahmad et al., 2013; Amanat et al., 2017; Ahmad et al., 2012). In this study, we focused on Kelulut honey (stingless bee honey) because it has been proven to contain highest concentration of antioxidants as compared to other types of honey (Nweze et al., 2017; Selvaraju et al., 2019). Besides, Selvaraju et al. (2019) have performed analysis on various types of honey from West Coast of Malaysia and found that stingless bee honey from *Trigona itama* has the highest antioxidant potential with the highest phenolic and flavonoid contents as compared to *Apis melifera* (honeybee).

Furthermore, as a natural product possessed high antioxidants, Kelulut honey (KH) has been assessed to reduce the development of aberrant crypt foci (ACF) in rat induce with colon cancer. In the study, ACF has been used as biomarker to identify the progression of development of colon cancer. It showed that KH has possessed chemopreventive properties as it successfully reduced the risk of cancer development induced by carcinogenic compound (Latifah et al., 2016). Additionally, Latifah et al. (2016) also reported that KH was not toxic to the rat since the level of blood profile parameters, liver enzymes and kidney functions was in normal range. Since KH was reported to have strong antioxidant activities as well as proven to be not toxic in animal study, it could be one of the potential radioprotective agent from natural resources.

Zebrafish (*Danio rerio*) is a powerful vertebrate model system for evaluating potential radiopotectant agents. It is because the zebrafish are rapidly bred, easy to maintain in the laboratory and the transparent visualization of the embryo allows the large-scale screening of therapeutic agents such as ionizing radiation and its modifiers (McAleer et al., 2005). In previous studies, several therapeutic agenst have been tested on the zebrafish model to observe for radioprotective activities and there were amifostine and fullerene nanoparticle DF-1 (McAleer et al., 2005), epicatechin compound (Shin et al., 2014), and mistletoe extract (Rim et al., 2019). Most of the radioprotectant studies only focused on survival and abnormalities developed in the zebrafish embryos. In the present study, we investigated the phenotypic changes in the zebrafish embryos during the development as well as the expression of selected proteins for DNA damage (γ-H2AX) and apoptosis (caspase-3) evaluation.

## 1.2. Objectives

The general objective of the study was to determine the protective properties of Kelulut honey (KH) in zebrafish embryo exposed to gamma irradiation.
The specific objectives of this study were:

1. To determine the radiosensitivity of zebrafish embryo exposed to different dose of gamma rays.

2. To determine the toxicity and $LC_{50}$ of KH in zebrafish embryo.

3. To determine the effects of KH treatment on the irradiated and bystander zebrafish embryos.

## 1.3. Hypothesis

KH as a potential radioprotectant is expected to increase the survival rate, reduce the abnormalities and lower the expression of DNA damage and apoptosis proteins in the zebrafish embryos.

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## BIODATA OF STUDENT

Mohd Noor Hidayat bin Adenan was born on 6th April 1985 in Pontian, Johor and later moved to Puchong, Selangor. He received his primary school education at Sekolah Kebangsaan Puchong Perdana. He continued his secondary school education in Sekolah Menengah Kebangsaan Agama Maahad Hamidiah, Kajang (Form 1 to 3) and later in Sultan Alam Shah Islamic College, Klang (Form 4 to 5). He completed his Sijil Pelajaran Malaysia (SPM) in the year of 2002. He was then offered to pursue Diploma in Medical Laboratory Technology in Universiti Malaya in the year of 2003 to 2006 with scholarship by Universiti Malaya Medical Centre. He has experience working as Medical Laboratory Technologist from 2006 to 2013. While working as a Medical Laboratory Technologist, he continued his study in Long Distance Learning Centre, Universiti Sains Malaysia in 2009 to 2013 and graduated in Bachelor of Science (Biology) (Hons). He was awarded as a Dean List Student during his final year of study in Universiti Sains Malaysia. In 2014, he got an offer to work at the Malaysian Nuclear Agency under the Ministry of Science, Technology and Innovation and he is now working at the agency as a Research Officer until the present day. He is at present a Master Science student of Universiti Putra Malaysia in Medical Biotechnology under the supervision of Associate Professor Dr. Latifah Saiful Yazan.

## LIST OF PUBLICATIONS

Mohd Noor Hidayat, A., Latifah, S. Y., Annie, C., Nur Fariesha, M. H., Suzita, M. N., Shuhaimi, S., Farah Jehan, A. B. & Khairuddin, A. R. (2021). Radioprotective effects of Kelulut honey in zebrafish model. Molecules, 26(6), 1–26.

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