



Systematic Review Summary of Various Extracts and Bioactive Compounds Potential in Increasing Radiation Efficacy in Human Cancer Cell Lines

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Background and Objective

- Cancer cells radioresistance still leave a problem for radiation oncologist, and chemotherapy administration as radiosensitizer is a way to increase therapeutic ratio.
- Many of Indonesia rich biodiversity have shown in vitro and in vivo (animal) anticancer effect:
 - Soursop (*Annona muricata* L.)¹
 - Red algae (*Eucheuma cottonii*)³
 - Bioactive compounds (piperine,² and gallic acid /3,4,5-trihydroxybenzoic acid⁴).
- Nevertheless, there is still a lack of study observing role of them as radiosensitizer

Methods

Mixed method review:

- Systematic review to assess the pathways used by extract/compounds,
- Continued by literature review to analyse the effects of the pathway inhibition/activation to radiation.

On various cell lines:

- Annona muricata* 20 studies, at least 10 related pathways to radiation, 3 opposite pathway¹
- Piperine 24 studies, 8 related pathways²
- Eucheuma cottonii* 13 studies, 4 related pathways, 1 opposite pathway³

On prostate cancer cell lines:

- Gallic acid, 11 relevant studies, 6 related pathways⁴

Results and Discussion

- Several substances activate/inhibit similar pathways in producing their anticancer effects.
- Among the most effective pathway that occupied by substances is cell cycle arrest, caspases, Bcl-family proteins pathway, and survival pathways.^{1,2,3,4}
- While referring certain pathways there is still inconsistency that reported by different studies (grey code).
- Annona muricata* is among the substances that have been reported by many studies.
- There are still many rooms for research using Indonesian original plant extract

	Consistent data from primary studies
	Conflicting data from primary studies
	The substance will contrarily decrease radiosensitivity
	No report or studies on the substance regarding the pathway

Pathways that could lead to <u>radiosensitization</u>	Extract / bioactive compounds			
	<i>Annona muricata</i>	Piperine	<i>Eucheuma cottonii</i>	Gallic Acid
Increased reactive oxygen species (ROS) formation				
Cell cycle inhibition (G0/G1 and G2/M phase) and prevention of DNA repair				
Regulation of Bcl-2 family proteins				
Loss of mitochondrial membrane potential				
Activation of caspase 3/7 and caspase 9				
Survival pathways	Suppressed nuclear factor kappa-B(NF-kB) translocation		E. cottonii increases NF-kB	
	Downregulation of molecules related to hypoxia and glycolysis (HIF-1, GLUT1, HKII, LDHA)			
	Downregulation of PI3K, Akt & ERK, mTOR			
	Downregulation of cyclin D1, (ERK1/2), and STAT3			
	Suppressed Hedgehog signaling			
	PD1/PDL-1			
	Suppressed PERK-eIF2 α	A. muricata increases PERK-eIF2 α		
Reduced proliferating cell nuclear antigen (PCNA)				
Immunomodulation				
Migration prevention / anti-metastasis by <u>Wnt</u> - β catenin inhibition				
Reduced Notch transmembrane protein	A. muricata increases Notch			
Reduced TNF- α	A. muricata increases TNF- α			

Conclusions

- Our mixed method review reveals radiosensitizing potential and helps sorting out extract / bioactive compound to undergo the next research steps.
- The substance with the most reported related pathways should be a good candidate for radiosensitizer.
- As a validation of our findings and a proper step of drug development, we suggest an in vitro study using human cancer cell line.

References



- [Accepted manuscript] Wijaya DA, Louisa M, Wibowo H, Taslim A, Permata TB, Handoko, et al. Future potential of *Annona muricata* L. extract and its bioactive compounds as radiation sensitizing agent: proposed mechanisms based on systematic review. *J Herbm Pharm*. 2021;10(1):x-x. doi: 10.34172/jhp.2021.xx.
- [Submitted Manuscript] Taslim A, Wijaya DA, Louisa M, Handoko, Permata TBM, Kodrat H, et al. The potential role of piperine as radiosensitizer in cancer treatment. *Indonesian J Pharm*.
- [Accepted Manuscript] Putri TP, Dewi IATK, Permata TBM, Nuryadi E, Kodrat H, Wibowo H, et al. A mini systematic review: *Eucheuma cottonii*, a red algae, as a radiosensitizer? *Tropical J Natural Product Research*.
- [Accepted Manuscript] Cahyono AT, Louisa M, Permata TBM, Handoko, Nuryadi E, Kodrat H, et al. The potency of gallic acid as a radiosensitizer on human prostate cancer: A systematic review of preclinical studies. *Malaysian J Med Health Sci*