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

Soehartati A Gondhowiardjo[1], Agung T Cahyono[1], Aslim Taslim[1], Tisa P Putri[1], Handoko[1], Henry Kodrat[1], Sri M Sekarutami[1], Endang Nuryadi[1], Tiara BM Permata[1], David A Wijaya[1]

[1]Faculty of Medicine, Universitas Indonesia – Cipto Mangunkusumo National General Hospital – Jakarta, Indonesia

Introduction

Despite technological advances in cancer treatment especially in radiotherapy, cancer cells radioresistance still leave a problem for radiation oncologist. In line with that, many efforts are being made in to increase therapeutic ratio, in order to reduce toxicity to surrounding healthy organ and increasing local/locoregional control in tumor. One among the most popular strategy to boost the radiation efficacy is using combination of chemotherapy and radiotherapy, known as chemoradiation. As a tropical country, Indonesia has a rich biodiversity. Many plants contain a great future potential as therapeutic agents, e.g. soursop (Annona muricata L.) and red algae (Eucheuma cottonii). On the other hand, isolated active substances contained in many types of plants like piperine and gallic acid are also interesting because they could provide more specific and consistent data.

HCLL is a basic cancer cells model, which allows a research in a limited simplified controlled environment. We are also able to make a genetic engineering in HCLL. In vitro HCLL has several similarities with in vivo cancer cells, i.e. uncontrolled growth (oncogenic), unresponsiveness to anti-growth signal, cell cycle checkpoint avoidance, immortality, loss of negative feedback, and invasive characteristics. After a cell receives ionizing radiation, several changes involving plentiful of pathways and proteins known as cellular response happen. There are various pathways/proteins that could be used to increase the radiation potential.

Objectives

In the present systematic review (mixed method review), we evaluate the possibility of several extracts and bioactive compounds in increasing radiation efficacy in human cancer cell lines (HCCL). Several extract and bioactive compounds have been collected. They are *Annona muricata* leaves extract, gallic acid, piperine, and *Eucheuma cottonii* extract. Many studies have reported their anticancer effect on numerous HCLL. Unfotunately, there is a lack of studies which reported their potential to increases the radiation efficacy.

Materials and Methods

We firstly performed a systematic review to assess the pathways used by extract/compounds to exert their anticancer effects. After that we carried out literature review to analyse the effects of

that the pathway inhibition/activation bring to the radiation effectiveness. This method is recognized as mixed method review.

From Annona muricata[1] review, we obtained 20 studies, and compiled at least 11 related pathways that will increase the radiosensitivity. There are 24 pre-clinic studies relating to piperine and 13 studies relating to Eucheuma cottonii. In a systematic review of gallic acid, 11 relevant studies were found after selection. They reveal the anticancer pathways of gallic acid in prostate cancer cell lines and may enhance the radiosensitivity

Results

Our study found significant potential from several different substances. We that several substances activate/inhibit similar pathways in producing their anticancer effects. Sometimes there are still conflicting data from primary studies (marked by grey code). We compiled the data of the extract/bioactive compounds and the pathway related to radiosensitivity (see Table 1.).

Table 1. Pathways of observed substances in correlation with their radiosensitizing potential

		Extract / bioactive compounds			
Pathways that could lead to radiosensitization		Annona muricata	Piperine	Eucheuma cottonii	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, HKIL, LDHA)				
	Downregulation of PI3K, Akt & ERK, mTOR				
	Downregulation of cyclin D1, (ERK1/2), and STAT3				
	Suppressed Hedgehog signaling				
	PD1/PDL-1				
	Suppresed PERK-eIF2α	A. muricata increases PERK-eIF2α			
	Reduced proliferating cell nuclear antigen (PCNA)				
Immunomodulation					

Migration prevention / anti-metastasis by Wnt-βcatenin inhibition				
Reduced Notch transmembrane protein	A. muricata increases Notch			
Reduced TNF-α	A. muricata increases TNF-α			

	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

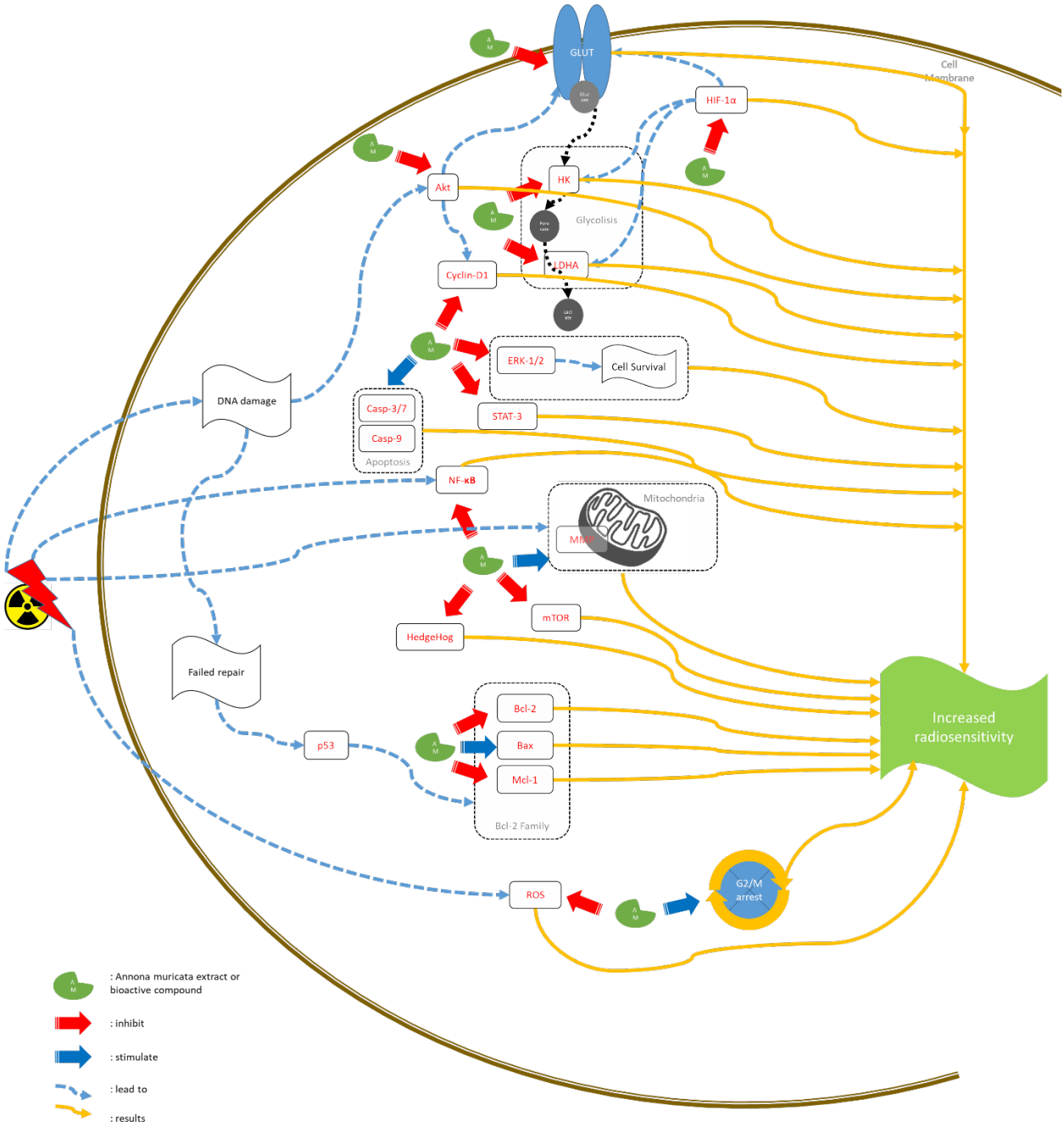

Figure 1. Predicted pathways that can be used by Annona muricata and its bioactive compounds to increase cancer cell radiosensitivity

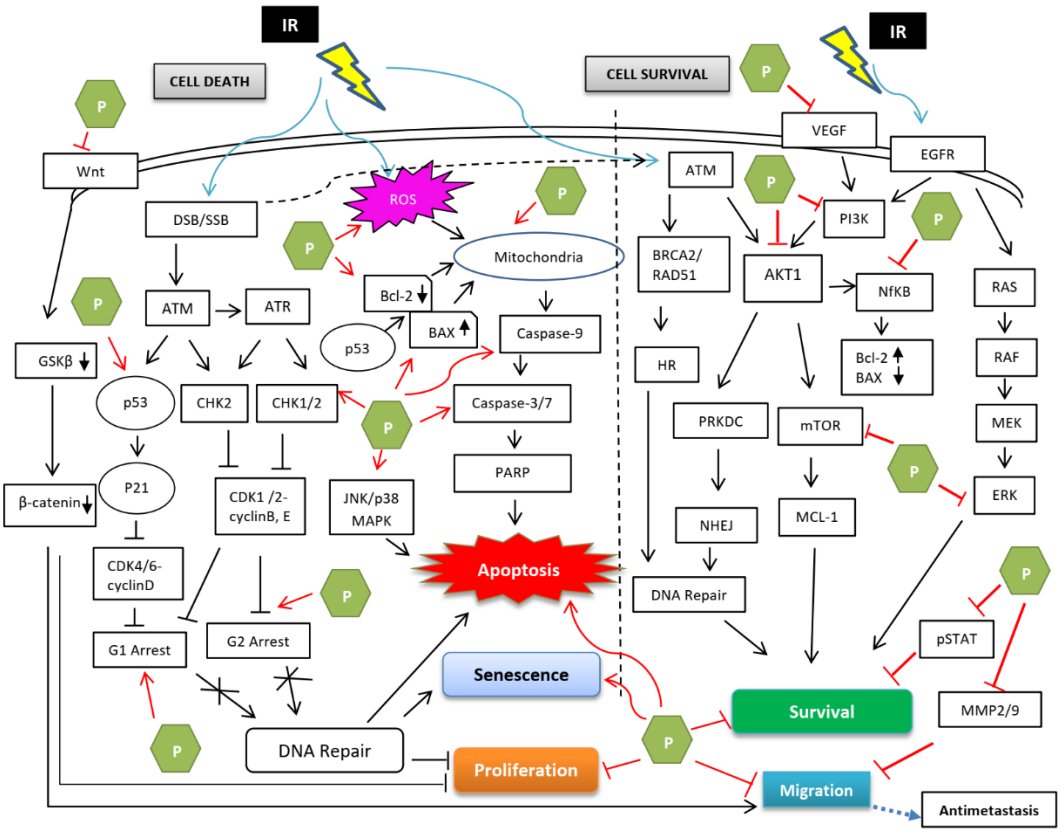

Figure 2. Potential role of Piperine in radioresistant tumor pathways

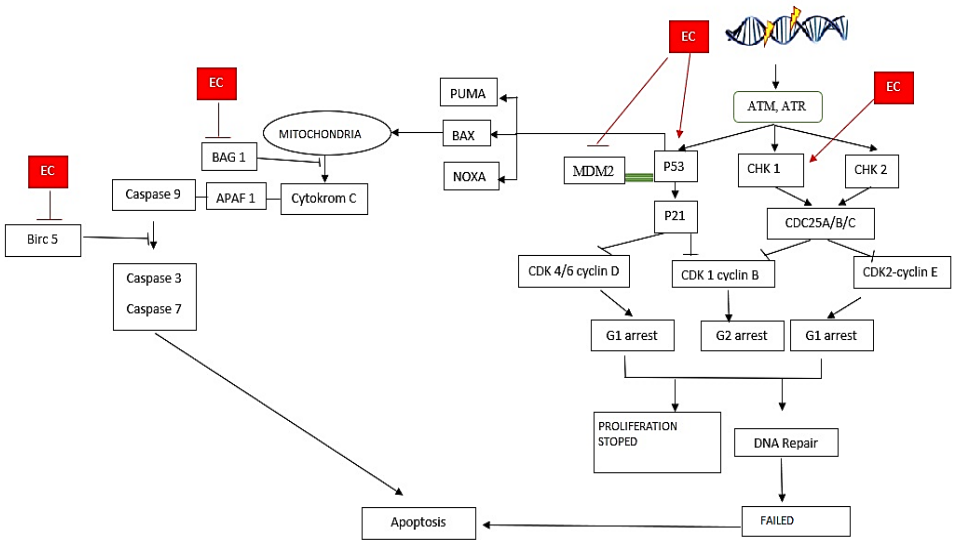

Figure 3. Radiosensitizer mechanism of Eucheuma cottonii

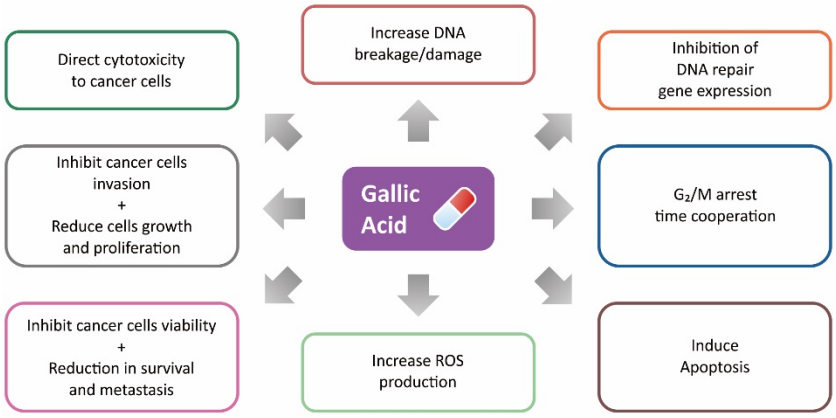

Figure 4. Summary of radiosensitization mechanism by gallic acid

Conclusion

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

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