REVIEW ARTICLE

Current Research on Biosciences and Biotechnology **2** (2) 2021 109-113

Current Research on Biosciences and Biotechnology

www.crbb-journal.com

The activity of bioactive compounds against several diseases by modulating autophagy

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ABSTRACT

Several bioactive compounds derived from Indonesia plants, such as xanthorrhizol, gingerol, and pinostrobin are the major compound in a certain plant. They have some pharmacological activities against several diseases, such as inflammation, tumor, and cancer, and modulate other mechanisms. One of them is one of programmed cell death called autophagy. The regulation involves several pathways on upstream and downstream of the autophagy mechanism and affects its activity. Each of the compound has different site of target when it comes to different case of diseases. Here we explained how the bioactive compounds regulate autophagy against several diseases.

Article history:

Received 29 Jan 2021
Revised 9 Feb 2021
Accepted 14 Feb 2021
Available online 28 Feb 2021

Keywords:

Zingiberaceae
xanthorrhizol
gingerol
pinostrobin
autophagy

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DOI: 10.5614/crbb.2021.2.2/WIWB7317

1. Introduction

Indonesia is a tropical country that has abundant sources of plants and herbal medicines. These plants contain some of the key compounds which are found as a majority of each plant to make them unique and proven to have some activities against diseases. The regulation of certain compounds to the medication of diseases targeting molecular responses is involved several cellular pathways regarding the diseases and the compound itself. Moreover, the regulation to suppress the diseases also affected by the natural mechanism of one of programmed cell death called autophagy (Glick et al., 2010).

Autophagy is a process of cell survival by the degradation of damaged organelles (Qomaladewi et al., 2019). It plays dual roles in tumor suppressor as well as tumor promotion: when it is repairing damaged tumor by targeting autophagy-related proteins, such as Beclin-1, UVRAG, Bif-1, and ATGs, and repairing mitochondria to inhibit ROS production; in the other hand, it plays as tumor promotion by targeting mutation of RAS, which dependently activates autophagy to induce tumor growth (Marinković et al., 2018).

Here we focused on some compounds which are the key compounds of the identity plants in Indonesia and the potential regulation by the presence of the compound to the regulation of autophagy against several diseases.

2. Xanthorrhizol

Xanthorrhizol (XNT) (Fig. 1a) is one of the key compounds found in *Curcuma xanthorrhiza* Roxb. (Java turmeric) which is in a group of sesquiterpenoid, bisabolene-type (Kang et al., 2009). It has some biological activities against several diseases, such as cancers (Kang et al., 2009; Ismail et al., 2005; Cheah et al., 2006; Oon et al., 2015), diabetes (Nurcholis et al., 2018), inflammation (Oon et al., 2015; Kim et al., 2014; Lim et al., 2005), and neurodegenerative (Lim et al., 2005). It is targeting the apoptotic pathway to minimize the presence of cancer cells by up-regulating Bax and p53 in HeLa cells and breast cancer by modulating Bcl-2, p53, and PARP-1 induced apoptosis *in vitro* using MCF-7 human breast cancer cells (Ismail et al., 2005; Cheah et al., 2006). Induction of xanthorrhizol also takes place in targeting NAG-1 by the regulation of AKT/GSK3b/mTOR signalling pathway (Oon et al., 2015).

3. Gingerol

Gingerol (GIN) (Fig. 1b), known as 6-gingerol is a phenolic compound which abundantly found in ginger (*Zingiber officinale* Roscoe) fresh root. The other bioactive compounds which have already been found to have activities are 10-gingerol and 6-shogaol. According to the latest research, GIN has anti-cancer properties, such as 6-gingerol reduces tumor volume and weight in A549 lung carcinoma cells by increased the accumulation of ROS and iron resulting in cell death (Tsai et al., 2020). Potential activity of 6-gingerol also was found in cervix cancer by inducing apoptosis protein agents, such as caspase 3 and 6 (Lechner and Stoner, 2019; Ho et al., 2013) and PRPP; the ratio of Bax/Bcl-2; as well as reactivation of p53 (Zhang et al., 2017a), (Rastogi et al., 2015). Another bioactive compound of gingerol, 10-gingerol, was found to induce apoptosis in breast cancer by targeting mitochondrial membrane permeabilization (MMP), and caspase-independent

apoptosis (CIA) by its analog SSi6 (Luna-Dulcey et al., 2018; Bernard et al., 2017). 10-gingerol (Fig. 1c) is also found as an anti-neuroinflammatory agent greater than 6-gingerol in LPS-activated BV2 microglia in inhibiting some of the pro-inflammatory genes' secretion, such as IL-6, IL-1β, TNF-α, iNOS, and protein level of iNOS (Ho et al., 2013). Another study is cervical cancer inhibition by 10-gingerol which targeting AMPK activation (Zhang et al., 2017b). Moreover, the regulation of Nrf2 also occurred in diabetes by the presence of 6-gingerol resulting in inhibition of Chronic Myeloid Leukemia (CML) (Sampath et al., 2017).

4. Pinostrobin

Pinostrobin (PN) (Fig. 1d) is one of the most flavones found in fingerroot (*Boesenbergia rotunda*) and honey which is commonly potential as an antioxidant and contribute against several diseases (Fahey and Stephenson, 2002; Chahyadi et al., 2014; Patel et al., 2016; Atun et al., 2017; Jadaun et al., 2019). Even though there are few numbers of reports regarding pinostrobin, some are reported to have roles to some cancers, such as in breast cancer by binding with estrogen receptor and fibrosarcoma by upregulating the expression of p53 and decreasing activation of VEGF angiogenesis (Le Bail et al., 2000; Parwata et al., 2015). It also has a role as a neuroprotector against Alzheimer's Diseases (AD) by increasing the ratio of Bcl-2/Bax ratio in PC12 cells, leading to apoptosis (Xian et al., 2012). Another study of pinostrobin activity to AD was also found by inhibition of Beta secretase enzyme (BACE1) which results in inhibition of β-amyloid peptide formation (Youn and Jun, 2019).

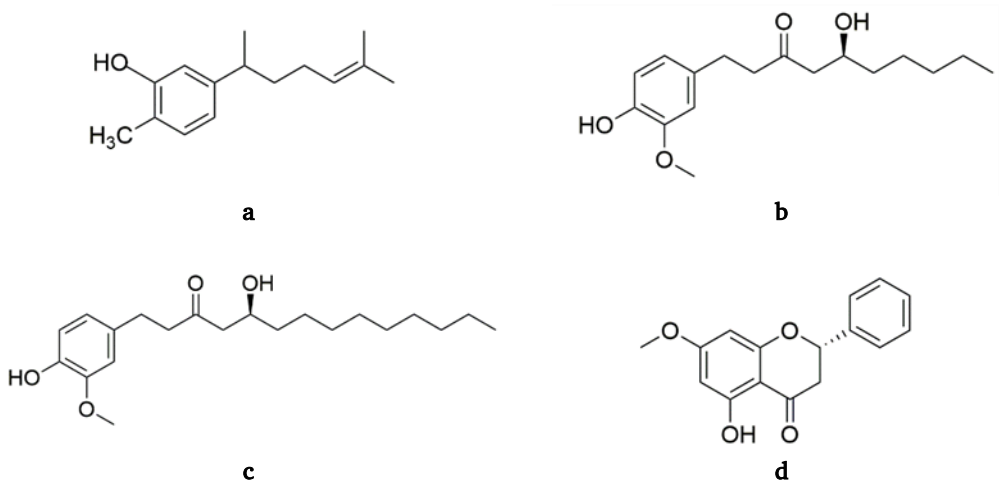

Fig. 1. The chemical structure of the bioactive compounds derived from Indonesian medicinal plants; a. xanthorrhizol; b. 6-gingerol; c. 10-gingerol; d. pinostrobin

5. Potential approach of the bioactive compounds to regulate autophagy

As explained in the review above, those three potential bioactive compounds could treat several diseases (Table 1), indicating the existence of cross-links between several diseases and autophagy by involving several pathways. For example, by targeting p53, which is a tumor suppressor gene, resulting in tumor cell death and activation of autophagy in the survival cells (Amaravadi et al., 2007). In case of tumor or cancer cells, lack of p53 induces stress to the cells and activates autophagy as the way the cells survive (White, 2016).

Some reports indicate the role of the bioactive compounds to regulate the expression of Bcl-2 and Bax. Bcl-2 is known as an anti-apoptotic protein that binds to Beclin-1 to inhibit autophagy (Fan and Zong, 2013; Pattingre et al., 2005). The formation of the Beclin-1 complex as the response of stress conditions leading to the activation of autophagy (macroautophagy) (Qomaladewi et al., 2019). The abundance of Bcl-2 regulates Mitochondrial Outer Membrane Permeabilization (MOMP) and induces Bax relocalization to mitochondria (Teijido and Dejean, 2010). Furthermore, when Bax is activated, cytochrome C is released and initiate apoptosis by the activation of caspase (Westphal et al., 2011). Transcription of Bax also can be induced by p53 (Hemann and Lowe, 2006).

Table 1. The activities of the bioactive compounds derived by Indonesian medicinal plants against several diseases

Bioactive compound	Type of diseases	Molecular target(s)	References
Xanthorrhizol	Cervix cancer	Bax and p53	Ismail et al. (2005)
	Breast cancer	Bcl-2 and PARP-1	Cheah et al. (2006)
		NAG-1 (in AKT/GSK3b/mTOR pathway)	Oon et al. (2015)
Gingerols			
6-gingerol	Lung tumor	ROS accumulation and iron (tumor cell death)	Tsai et al. (2020)
	Cervix cancer	caspase 3 and 6	Lechner and Stoner (2019), Ho et al. (2013)
		PRPP, Bax/Bcl-2 ratio, reactivation of p53	Zhang et al. (2017b), Rastogi et al. (2015)
10-gingerol	Diabetes	Nrf-2	Sampath et al. (2017)
	Breast cancer	MMP	Luna-Dulcey et al. (2018)
		CIA	Bernard et al. (2017)
	Neuroinflammatory	pro-inflammatory genes and proteins	Ho et al. (2013)
	Cervix cancer	AMPK activity	Zhang et al. (2017a)
Pinostrobin	Breast cancer	estrogen receptor	Le Bail et al. (2000)
	Fibrosarcoma	p53 and VEGF angiogenesis	Parwata et al. (2015)
	Alzheimer's Diseases	Bcl-2/Bax ratio	Xian et al. (2012)
		BACE1	Youn and Jun (2019)

The occurrence of autophagy regulation by PARP-1 through deficiency of ATP due to the rapid depletion of NAD+, leading to activate LKB1 to activate autophagy in AMPK/mTOR pathway (Huang and Shen, 2009). This approach could be addressed as one of the ways of cell death induction-based chemotherapy (Muñoz-Gámez et al., 2009). The activation of AMPK leading to autophagy activation also takes place by the presence of vascular endothelial growth factor (VEGF) in mTOR-independent way where the downstream is ULK 1/2 (Spengler et al., 2020).

When autophagy deficiency occurs, there will be an accumulation of p62 as a marker of protein aggregates which potentially the beginning of neurodegenerative diseases (Irvine et al., 2008; Komatsu et al., 2007). As p62 increased, Nrf-2 transcription factor is up-regulated by the interaction between p62 and Keap1, which decreased the ability of Keap1 to degrade Nrf-2 in ubiquitination and proteasomal degradation manner (Lau et al., 2010). Nrf-2 then regulates antioxidant activity in response to ROS accumulation, promoted by ARE (Zhang, 2006). Deficiency of Nrf-2 resulting in oxidative stress by H_2O_2 to initiate autophagy (Ramsey et al., 2007). This is showing the looping mechanism of autophagy in Nrf-2-Keap1 signalling pathway.

Another phenomenon in neurodegenerative diseases, such as AD occurs by involving the activity of BACE1 to up-regulate the formation of β-amyloid peptides (Das and Yan, 2017). BACE1 usually degrades by lysosomal degradation and autophagy could take over this through trafficking into autophagosome (Chen et al., 2015; Feng et al., 2017). Therefore, this is one of the pivotal targets of AD treatment due to its specificity.

Nowadays, there is a new type of programmed cell death called ferroptosis correlated with the accumulation of iron and lipid peroxidation, particularly resulting in oxidative cell death and activation of autophagy. In the case of lung cancer, as explained in the treatment by 6-gingerol, inhibits USP14 as cancer therapy will be resulting in the induction of ferroptosis, concomitantly with autophagy in Beclin1 dependent manner (Tsai et al., 2020). This approach would be potential for cancer therapy in several types of cancer since the strong correlation with ROS and iron accumulation in the cancer cells.

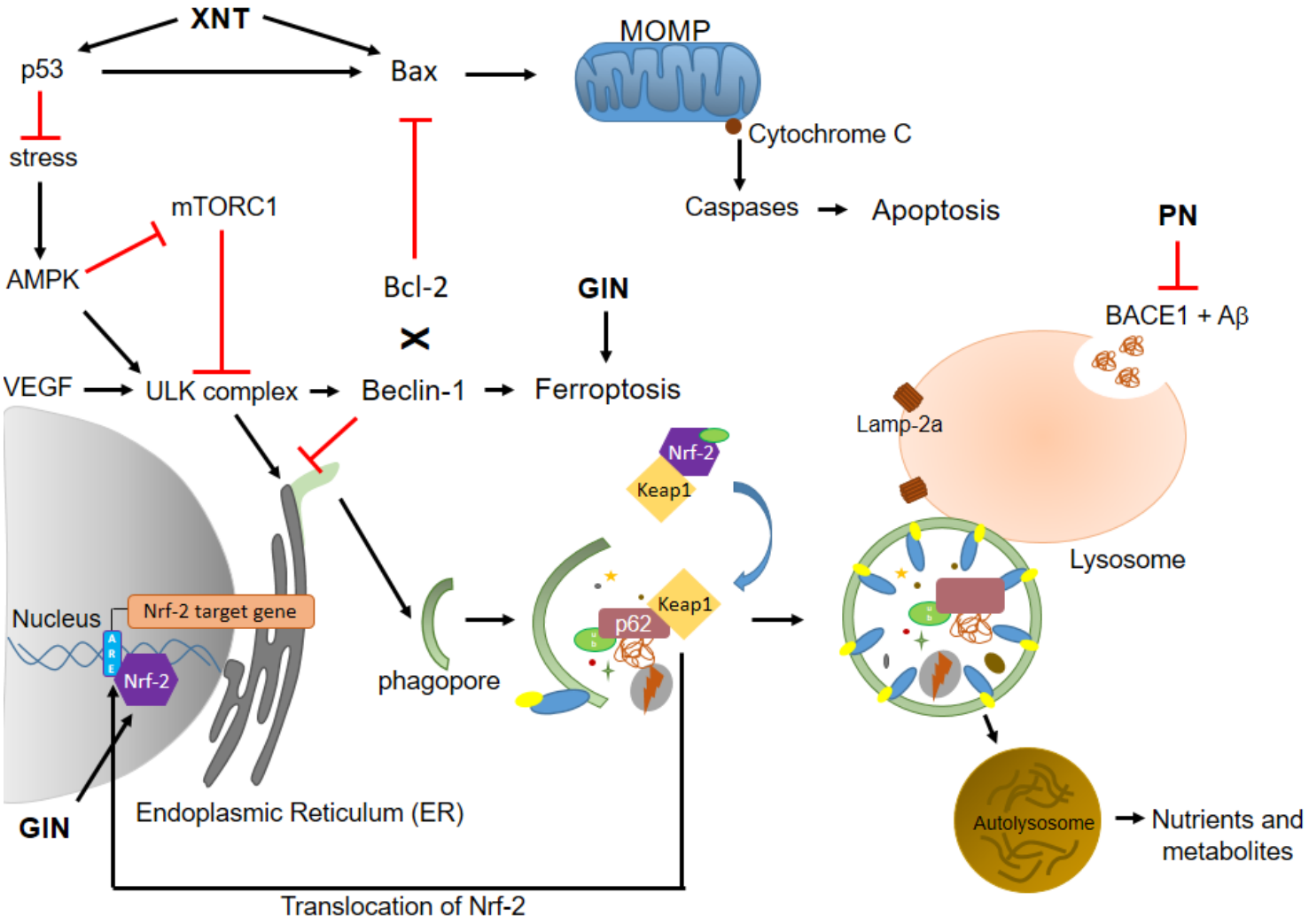

Fig. 2. The mechanism of autophagy affected by the other mechanisms and its regulation by the bioactive components. Xanthorrhizol regulate p53 and Bax resulting in autophagy and apoptosis activation; gingerol is targeting Nrf-2 translocation to modulate Nrf-2 transcription factor and ferroptosis, whereas pinostrobin inhibits BACE1 to induce β-amyloid formation.

6. Conclusion

In many cases, the bioactive compounds are targeting the upstream of autophagy, which is not specific to state the implication of these compounds to have activity against some diseases in the case of autophagy (Fig. 2). Nevertheless, in the future, it is potential to figure out the mechanism of the bioactive compounds in the autophagy-related proteins' manner as one way of the treatment of the diseases.

Acknowledgement

This research was supported by University Center of Excellence for Nutraceuticals, Bioscience and Biotechnology Research Center, Bandung Institute of Technology.

Conflict of interest

The authors declare there is no conflict of interest in this study.

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