Potency of Bioactive Compound of Rice Bran for Colon Cancer Prevention

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Abstract
Colon cancer is the second leading cause of death in the world. Bioactive compounds in rice bran have a very active role as antiproliferation of colon cancer cells such as ferulic acid, p-coumaric acid, caffeic acid, gallic acid, protocatechuic acid, sinapic acid, tricin, luteolin, apigenin, myrecitin, rutin, isorhamnetin, γ-oryzanol, γ-tocopherol, δ-tocopherol, γ-tocotrienol, β-sitosterol, phytic acid, and hemicellulose. Mechanism of the bioactive compounds in cells varied, including modulation of a cell cycle, activation of immune cells, damage of a lipid layer and mitochondrial membrane, activation of caspase proteins, inhibition of protein cell tumor invasion, metastasis, and angiogenesis, and also acts as an antioxidant. Therefore, the existence of the scientific studies results of this review with the potential availability of adequate rice bran in Indonesia is very potential to be developed.

Introduction
Bioactive compounds are phytochemicals that can be found in food, serves to modulate metabolic processes to improve health. The bioactive compounds in rice bran have been widely known that have a role in reducing several diseases such as hyperlipidemia (Um et al., 2013), antiproliferation in cancer cells (Hui et al., 2010; Zulfafamy et al., 2018; Islam et al., 2017; Ghoneum & Agrawal 2011), antidiabetic (Adriansyah et al., 2006; Noviasari et al., 2019; Kurniawati et al., 2016), chronic kidney disease and acute coronary syndrome (Rashid et al., 2015).

Rice bran is a by-product of the rice milling process. In the process of rice milling, 10% of rice bran will be produced. The potential of rice bran that produced was estimated at 5.65 million tons in Indonesia in 2018 (Badan Pusat Statistik, 2018). However, the use of rice bran in Indonesia is generally still limited to animal feed (Tuarita et al., 2017).

Several bioactive compounds in rice bran had the potency to inhibit colon cancer cells, that were specifically reported, namely γ-tocotrienol (Xu et al., 2012), γ-oryzanol (Kim et al., 2012), and ferulic acid (Janicke et al., 2011). Inhibition of cancer cell proliferation by utilizing the potential of rice bran bioactive compounds is preventive prevention (Law et al., 2017), while curative prevention is a type of treatment that has long been applied, such as surgery, radiotherapy, and chemotherapy. Chemotherapy treatment is often reported to cause effects on other organs (Focaccetti et al., 2015). The chemotherapy agents have been commonly used, in patients with colon cancer are leucovorin, capecitabine, irinotecan,
oxaliplatin, and 5-fluorouracil (Nasrallah & Sibai, 2014).

Colon cancer itself was ranked the second highest cause of death in the world in 2018 (Bray et al., 2018). While in Indonesia, ranked the third highest (equivalent to the percentage of people with lung cancer), with the number of incidents in 2018 of 15,245 people, and will continue to increase until 2040 with an estimated number of 27,354 people, based on the 2018 Global Cancer Data (IARC, 2018). This disease is caused by two main factors, namely internal factors (5-10%) including genetic factors, and external factors (90-95%) such as stress, obesity, radiation, and bad dietary as the biggest contributing factor that is 30% to 35% (Anand et al., 2008). The effort of preventing cancer can be done, among others, by consuming functional food products. Rice bran which contains the bioactive compound can be used as ingredient for development of functional food products.

This article will review the potential of bioactive compounds in rice bran as the prevention of colon cancer. Scientific studies of bioactive compounds and their mechanisms for colon cancer will be reviewed in this article, which will be shown in the form of mapping. Furthermore, the development of rice bran as functional food will also be discussed to provide an illustration of the extent rice bran has been applied as a functional food.

Bioactive Compounds in Rice Bran and its Function

Even though rice bran is a byproduct of the rice milling process, it contains many essential nutrients such as vitamins, minerals, amino acids, antioxidants (Younas et al., 2011), bioactive compounds, fats (Alauddina et al., 2017), and dietary fiber such as β-glucan, pectin, and gum (Prasad et al., 2011). Fatty acids are dominated by linoleic (31-33%), oleic (37-42%), palmitic (21-26%), and also high in content of polyunsaturated fatty acids, which are known to be good for health (Oliveira et al., 2011).

Antioxidants have been reported that has a role in protecting cell damage due to oxidative stress resulting from the formation of free radicals, the oxidative stress is the main cause of cancer cases (Kumar, 2014). Groups that act as antioxidant compounds are phenolic acids, anthocyanins, flavonoids, tocotrienols, tocopherols, γ-oryzanol, and phytic acid (Goufo et al., 2014). These groups are found in rice bran. The amount of bioactive compound and nutrient content in rice bran can be seen in Table 1.

Pigmented rice bran has been reported that is rich content in anthocyanin and proanthocyanidin. Both of them have a contribution to pigmented of rice, antioxidant (Limtrakul et al., 2019; Anggraini et al., 2015), anti-inflammatory (Limtrakul et al., 2016; Xia et al., 2006), and anthocyanin also act as cytotoxic activity (Pratiwi & Purwestri, 2017). Abdel-Aal et al., (2006) reported, the anthocyanin in black rice bran contained 3.276 mg/g and red rice bran contained 0.094 mg/g. While Hosoda et al., (2018) reported, that anthocyanin was only detected in black rice with the highest concentration, namely the Minenomurasaki cultivar (5.045,6 μg/g), while red rice was dominated by the proanthocyanidin component in the Yuyakemochi cultivar (3.060,6 μg/g). The variation in the amount of anthocyanin content is due to differences in rice cultivars and location of growth (Alauddina et al., 2017).

The compound of β-carotene and lycopene have been reported that it very contributes to the reddish-brown appearance, and both of them are precursors of vitamin A, which can act as antioxidants in the biological system (Lamberts et al., 2016). β-carotene and lycopene are part of the carotenoids. These carotenoids are able to bind singlet oxygen and to trap free peroxy radicals, and it is called photoprotective agents (Manickavasagan et al., 2017). Brown rice bran was reported that contains dietary fiber which was four times higher than the white rice (Sun et al., 2010; Limtrakul et al., 2019), contained essential amino acids such as lysine (Limtrakul et al., 2019), and rich in content of vitamins, such as niacin (3.5-5.3), riboflavin (0.04-0.14), thiamine (0.29-0.61), and tocopherol (0.90 –2.50), units of measurement were shown here as mg/100 g of flour (Manickavasagan et al., 2017).

The bioactive component of γ-oryzanol which is present in rice bran (black, red, brown) was reported that had an antioxidant activity of 10 times higher than tocopherol, while
Table 1. Groups of bioactive compounds in rice bran

| Bioactive compound            | Column Header Goes Here | Reference                        |
|-------------------------------|-------------------------|----------------------------------|
|                               | Black       | Red       | Brown     |
| Phenolic acids                |              |           |           |
| Protocatechuic acid (mg/100g) | 6.18        | 5.31      | 2.87      | Ghasemzadeh et al. (2018) |
| p-coumaric acid (mg/100g)     | 33.35       | 24.53     | 16.71     | Ghasemzadeh et al. (2018) |
| Ferulic acid (mg/100g)        | 28.04       | 23.83     | 17.79     | Ghasemzadeh et al. (2018) |
| Cinnamic acid (mg/100g)       | 25.53       | 15.33     | 9.61      | Ghasemzadeh et al. (2018) |
| Syringic acid (mg/100g)       | 24.40       | 21.50     | 14.42     | Ghasemzadeh et al. (2018) |
| Sinapic acid (µg/g)           | 252.10      | 209.80    | 258.7     | Laokulilok et al. (2011)  |
| Gallic acid (µg/g)            | 161.10      | 39.00     | 25.10     | Laokulilok et al. (2011)  |
| Hidroxybenzoic acid (µg/g)    | 443.30      | 52.50     | 68.90     | Laokulilok et al. (2011)  |
| Vanillic acid (mg/100g)       | 36.930      | 13.83     | 0.98      | Pang et al. (2017)         |
| Isoferulic acid (mg/100g)     | 7.340       | 8.39      | 12.34     | Shao et al. (2014)         |
| Caffeic acid (µg/g)           | 16.900      | 24.20     | -         | Sumczynski et al. (2016)   |
| Flavonoids                    |              |           |           |
| Apigenin (mg/100g)            | 15.31       | 6.39      | 4.22      | Ghasemzadeh et al. (2018) |
| Luteolin (mg/100g)            | 10.72       | 7.74      | 2.35      | Ghasemzadeh et al. (2018) |
| Catechin (mg/100g)            | 22.05       | 15.90     | 8.96      | Ghasemzadeh et al. (2018) |
| Myrecitin (mg/100g)           | 12.85       | 12.82     | 5.68      | Ghasemzadeh et al. (2018) |
| Quercetin (mg/100g)           | 15.55       | 9.27      | 2.87      | Ghasemzadeh et al. (2018) |
| Tricin (µg/g)                 | 10.00       | 2.40      | 2.00      | Poulev et al. (2017)       |
| Rutin (µg/g)                  | 2.80        | 4.10      | -         | Sumczynski et al. (2016)   |
| Isoflavonoids                 |              |           |           |
| Cyanidin-3-glucoside (µg/g)   | 2316.7      | 179.0     | ND        | Laokulilok et al. (2011)   |
| Peonidin-3-glucoside (µg/g)   | 245.7       | 9.10      | ND        | Laokulilok et al. (2011)   |
| Cyanidin-3-rutinoside (µg/g)  | 0.70        | ND        | -         | Huang & Lai (2016)         |
| Steroidal compounds           |              |           |           |
| γ-oryzanol(mg/g)              | 9.12        | 8.58      | 1.52      | Moongngram et al. (2012)   |
| α-tocopherol(µg/g)            | 43.57       | 44.00     | 41.36     | Moongngram et al. (2012)   |
| γ-tocopherol(µg/g)            | 35.31       | 25.00     | 37.97     | Moongngram et al. (2012)   |
| δ- tocopherol(µg/g)           | 4.28        | 4.30      | 0.25      | Huang & Lai (2016); Min et al. (2014) |
| α-tocotrienol(µg/g)           | 9.99        | 11.49     | 4.36      | Huang & Lai (2016); Min et al. (2014) |
| γ-tocotrienol(µg/g)           | 53.09       | 45.83     | 32.27     | Huang & Lai (2016); Min et al. (2014) |
| δ- tocotrienol(µg/g)          | 6.03        | 5.66      | 2.50      | Huang & Lai (2016); Min et al. (2014) |
| Others                        |              |           |           |
| Protein                       | 13.27       | 12.93     | 12.07     | Moongngram et al. (2012)   |
| Fat                           | 15.85       | 17.32     | 16.96     | Moongngram et al. (2012)   |
| Fiber                         | 12.68       | 12.11     | 11.77     | Moongngram et al. (2012)   |
| Phytic acid                   | 35.00       | 39.91     | 48.12     | Moongngram et al. (2012)   |

Information: ND = Not Detected
tocotrienol had antioxidant activity 40-60 times higher than tocopherol activity (Alauddina et al., 2017). These are detected much more in black rice bran. However, all rice bran types contain 4-hydroxy-3-methoxycinnamic acid, which is known to have antioxidative effects and photoprotective (Garcia-Conesa et al., 1999).

The Mechanism of Bioactive Compounds in Rice Bran as a Colon Cancer Prevention

The prevention mechanism of colon cancer cells by bioactive compounds in rice bran is reported very diverse, starting from acting as an antioxidant so that it can protect against free radicals, changing the cell cycle, cell antiproliferation, modulating the immune system, inducing apoptosis in the cascade pathway, and protecting the layers mucosa by influencing microbial transformation through high fiber content in rice bran (Henderson et al., 2012).

These mechanisms were also known different, both of the same or different groups of bioactive compounds, such as ferulic and p-coumaric acid, even though both were phenolic compound group, and capable to delay development in the Caco-2 colon cancer cell cycle, but through a different inhibitory pathway. Ferulic acid delayed on the S phase pathway, affected the centrosome central regulatory genes, and DNA damage checkpoint genes such as CEP2, CETN3, and RABGAP1. While p-coumaric acid induced the G2/M phase pathway and affected other cell cycle regulating genes, such as MYC, CDKN1A, PCNA, CDC25A, ODC1, CCNA2, and CCNB1 (Janicke et al., 2011). Bioactive compound of p-coumaric acid not only played a role in delaying the cell cycle, but it was also reported to have the inhibitory ability on other mechanisms. Supplementation of p-coumaric acid on albino male rats, which was given procarcinogens 1,2 dimethylhydrazine (DMH) could inhibit glucose-regulated protein (GRP78) which was an indicator of transformation into malignant cancer, besides that, p-coumaric acid was able to mediate apoptosis against unfolded protein response (UPR) activated, which was the key to the development of oncogenic by inhibiting the expression of p-p65 (NF-κB) and p-IκBα, and reduced inflammation characterized by the decreased cytokine expression, namely COX-2, IL-6, TNF-α and PGE2 (Sharma et al., 2018).

UPR activation was reported to be able to activate anti-apoptotic NF-κB, thus inhibiting apoptotic signals from p53 and inducing angiogenic activity through increased vascular endothelial growth factor (VEGF) (Yadav et al., 2014). The increase of VEGF would cause cancer cells to receive nutrient and oxygen supply so that it was pushed to grow faster, inhibition of VEGF was also known to be regulated by COX-2, 5-LOX (Kim et al., 2012) and GRP78 enzymes through VEGFR-2 mediating signals (Katamasaka et al., 2010).

Another component that is also reported to play a role in inhibiting colon cancer is γ-oryzanol. Giving γ-oryzanol as feed to Balb/c mouse transplanted by colon cancer cells CT26, was able to modulate the immune system by improving the function of phagocytosis in macrophages, released pro-inflammatory cytokines, tumor necrosis factor-α, IL-1β, and IL-6 by macrophages, increased the activity of natural killer cells (NK), reduced the number of blood vessels in cancer, suppressed vascular endothelial growth factor (VEGF) which was a marker of angiogenesis, and suppressed the COX-2 and 5-LOX enzymes (Kim et al., 2012). Phagocytosis is very important for cells to protect hosts against harmful foreign particles by swallowing and destroying them, and this process is very important as a form of immune response (Pavlou et al., 2017).

Other mechanisms of colon cancer cell inhibition are also reported, namely through the caspase cascade apoptosis pathway. This pathway can kill cancer cells without inflammation and damage to surrounding cells, by mediating by caspase which will produce an active signaling molecule, which acts as the main link in the regulatory network within the cell, so as to control cell death and inflammation (McIlwain et al., 2013). Apigenin (flavonoid group) was reported to be able to increase caspase-8 expression (initiator caspase), and caspase-3 (caspase executor) in HT-29 colon cancer cells, and could reduce cyclin D1 and rapamycin expression. Cyclin D1 acted as a protein that regulated cell cycles, while rapamycin was used as a clinical
| Bioactive compound | Cell/Animal model | Mechanism | Reference |
|-------------------|-------------------|-----------|-----------|
| Ferulic acid      | Caco-2, HT29-D4   | Delays the development of the cancer cell cycle especially in the S phase | Janicke et al. (2011) |
|                   | F344 Rats         | Reduces the formation of ACF (Aberrant Crypt Foci), reduces the incidence of colon tumors, and increases the activity of quinone reductase (detoxification enzymes) | Kawabata et al. (2000) |
| p-Coumaric acid   | Caco-2, HT29-D4   | Delays the development of the cancer cell cycle especially in the G2/M phase | Janicke et al. (2011) |
|                   | HT29; HCT15       | Inhibits the production of superoxide anion (O$_2^-$) and proliferation of cancer cells, decreases the cell adhesion, and movement of cancer cells | Bouzaiea et al. (2015) |
|                   | Wistar Rats       | Damages the lipid layer and mitochondrial membrane of cancer cells, and increases the oxygen production of reactive species (cancer cells are shrinking) | Jaganathan et al. (2013) |
|                   | Albino Wistar Rats| Induces the apoptosis by decreasing the expression of cytokines COX-2, IL-6, TNF-a, PGE2, p-p65 and p-IkBa, as well as inhibits GRP78 (Glucose Regulated Protein), and mediates apoptosis against active UPR (Unfolded Protein Response). | Sharma et al. (2017) |
|                   | HT29-D4           | Inhibits cancer cell adhesion, cell movement, superoxide anion (O$_2^-$) production, and proliferation | Bouzaiea et al. (2015) |
| Caffeic acid      | HCT15             | Damages the lipid layer and mitochondrial membrane in cancer cells, increases the oxygen production of reactive species, and induces apoptosis | Subramanian et al. (2016) |
| Gallic acid       | Colo320; SW480; | Suppresses oxidative stress, significantly reduces lipid peroxide, and significantly increases the concentration of enzymatic and non-enzymatic antioxidants | Giffon et al. (2010) |
| Protocatechuic acid| Caco-2            | Induces apoptosis, decreases cancer cell viability, and inhibits DNA synthesis | Zheng et al. (2002) |
| Trcin             | HTCA7             | Inhibits the activity of the COX-1 and COX-2 cyclooxygenase enzymes (proliferation enzymes), reduces the production of prostaglandin E2 (PGE2) | Cai et al. (2005) |
| Sinapic acid      | HT29; SW480       | Reduces the number of tumors, and reduces the amount of prostaglandin E2 (PGE2) | Cai et al. (2005) |
| Caffeic acid      | Xenograft Model Mouse | Increases the reactive production of oxygen species and lipid peroxides, damages the mitochondrial membrane in cancer cells, and induces apoptosis. | Balaji et al. (2014) |
| phenethyl ester; caffeic acid phenylpropyl ester | Caco-2, SW480; | Reduce the number of tumors; reduce PCNA, FASN, and MMP-9 | Chiang et al. (2014) |
| Luteolin          | Balb/c Rats       | Protects DNA from oxidative damage, and improves activity in cancer cells. | Ramos et al. (2010) |
|                   |                  | Induces the cell cycle to delay in the G2/M phase | Wang et al. (2004) |
|                   |                  | Acts as an antimetastatic agent by suppressing the production of MMP-9 and MMP-2 | Pandurangan et al. (2014) |
|                   |                  | Reducing lysosomal enzyme activity, inducing apoptosis by modulating Bcl2, Bax and Caspase-3 | Pandurangan & Ganapsam (2013) |
|                   |                  | Reduces MDF (Mucin Depleted Foci) and glycoconjugates levels | Pandurangan et al. (2012) |
| Compound       | Source(s) | Effect(s)                                                                                                                                                                                                 | Reference(s)               |
|----------------|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------|
| Isorhamnetin   | HT29; HCT116; SW480 | Reduces the number of tumors, controls the level of polyamines, and controls the proliferation of cancer cells through inhibition of Wnt/β-catenin and GSK-3β pathways. Also delays the cell cycle in the G1/M phase, inhibits the PI3K-Akt- mTOR (proliferation) pathway, decreases the protein phosphorylation of Akt (ser473), phospho-p70S6 kinase, and phospho-4E-BP1 (S74), and increases the expression of Cyclin B1 protein. | Ashokkumar & Sudhandiran (2011), Li et al. (2014) |
| Apigenin       | SW480; HCT15 | Inhibits the pathway signal of Wnt/β-catenin, thereby suppressing cell proliferation, migration, invasion, and tumor organoid growth.                                                                 | Xu et al. (2015)            |
| Myrecitin      | HCT115     | Increases the expression of mTOR and caspase-3 and caspase-8 proteins, and decreases the expression of rapamycin (mTOR) and cyclin D1 (CCND1).                                                               | Turktekin et al. (2011)    |
| Rutin          | Nude Mice (SW480 Cell Injection) | Reduces VEGF production in rat serum that contains cancer.                                                                                                                                               | Alonso-Castro et al. (2013) |
| γ-tocopherol   | HT29       | Reduces the potential in the mitochondrial membrane in cancer cells, resulting in the release of cytochrome c compounds that cause activation of caspase 3 (apoptosis). Reduces the amount of ACF (Aberrant Crypt Foci), decreases the amount of 4-hydroxyxenenal, nitrotyrosine, and expression of cyclin D1 in the colon, decreases prostaglandin E2 and 8-isoprostane in serum. | Rezaei et al. (2014), Guan et al. (2012) |
| γ-tocotrienol  | HCT116; HT29; Caco-2 | Suppresses dAIP-1, dAIP-2, survivin (tumorigenk protein) expressions; inhibits the expression of cyclin D1, c-Myc (cell proliferation protein) on HCT116 cells, inhibits expression of MMP-9, VEGF, ICAM-1, CXCR4 (tumor cell invasion protein, metastasis, and angiogenesis), and inhibits NF-kB activation (regulates antiapoptotic protein) in HCT116 cells | Prasad et al. (2016), Zhang et al. (2013), Xu et al. (2012) |
|                | SW620; HCT8 | Suppresses protein expression and Wnt/β-catenin signal, cyclin D1, and c-jun.                                                                                                                                                         |                            |
|                | HT29       | Suppresses the β-catenin/Tcf signal (by suppressing the expression of c-myc, cyclinD1 and survivin target genes), thereby inhibits growth and induces apoptosis                                                                 |                            |
|                | Xenograft Model Nude Mouse Transplantation Cell (HCT-116; SW620) | Suppresses protein expression and Wnt/β-catenin signal, cyclin D1, and c-jun.                                                                                                                                                         |                            |
| γ-tocotrienol  | F344 Rats  | Reduces tumor growth, and decreases the expression of Ki-67, cyclin D1, MMP-9, CXCR4, NF-kB-p65, and VEGF                                                                                                                                  | Prasad et al. (2016)       |
| δ-tocopherol   | F344 Rats  | Reduces the amount of ACF (Aberrant Crypt Foci), decreases the amount of 4-hydroxyxenenal, nitrotyrosine, and expression of cyclin D1 in the colon, decreases prostaglandin E2 and 8-isoprostane in serum. | Guan et al. (2012)         |
| γ-oryzanol     | Balb/c Mouse (CT-26 cell transplantation) | Activates natural killer cells, activates macrophages, and inhibits angiogenesis.                                                                                                                                                  | Kim et al. (2012)          |
| β-sitosterol   | COLO 320 DM | Increases DNA fragmentation and reactive oxygen production of species, suppresses expression of β-catenin and PCNA (marker of cell proliferation)                                                                                       | Baskar et al. (2010)      |
|                | Wistar Rats | Reduces the amount of ACF (Aberrant Crypt Foci) and CM (crypt multiplicity), acts as an antioxidant, and suppresses the expression of β-catenin and PCNA                                                                                     | Baskar et al. (2010)      |
| Phytic acid    | Sprague-Dawley Rats | Reduces the amount of ACF (Aberrant Crypt Foci)                                                                                                                                                                                   | Norazalina c. al. (2010), Shafie et al. (2013) |
| Hemicellulose  | F344 Rats  | Decreases β-catenin expression and COX-2, Reduces the number of tumors                                                                                                                                                          | Kawasaki et al. (2008)    |
pathological parameter in colorectal cancer patients (Turktekin et al., 2011).

The study of the potential of rice bran as an antiproliferation of colon cancer cells through the mechanism of bioactive compounds, can be seen more comprehensively from the results of in vitro and in vivo studies presented in Table 2. In vivo study studies are presented to strengthen the evidence that the bioactive component present in bran, also works effectively in inhibiting colon cancer cells in experimental animal.

The Development of Rice Bran as Functional Food

The development of functional food from rice bran in Indonesia is still very limited. Even though data collection of BPS-Statistics Indonesia, Rice production in 2018 was 56.54 million tons, which meant the availability of rice bran potential could reach 5.65 million tons (Central Bureau of Statistics, 2018), that matter make of the processing of rice bran into functional food, that will have a high economic value. Furthermore, the potential of health is also very promising because the content of bioactive compounds is varied, such as high phenolic acids content in nonpigmented rice (1.96 mg GAE/g), red rice bran (4.39 mg GAE/g), and black rice bran 6.65 (mg GAE/g), data were shown here as % dry weight (Moongngram et al., 2012), and also contain other bioactive compound such as γ-oryzanol, tocopherol, tocotrienol, anthocyanins, and flavonoids.

Some countries in the world such as the United States, Australia, and Japan have developed rice bran processed products to the commercial stage, such as rice bran cereal, rice bran dessert or energy drinks, rice bran tortillas, rice bran flakes, and rice bran oil. This situation is very different in Indonesia, which are generally still found are traditional foods, such as rice bran bangket, rice bran jenang or rice bran porridge (Widowati, 2001). Lack of public awareness about the benefits of rice bran, rice bran quality that has not been standardized, and the lack of downstream industries interested in developing rice bran, become obstacles in the effort to develop rice bran as a functional food (Tuarita et al., 2017).

There were some processed rice bran products that had actually been developed at a laboratory scale, such as tempe enriched by rice bran, so resulting in a total phenolic increased by 67% with a ratio of rice bran and soybean (4:6) (Cempaka et al., 2018). Chips products with the main ingredient of wheat flour mixed with bran-enriched soybean had increased protein content by 73% with a ratio of soybean flour and wheat flour (3:7) (Cempaka et al., 2018).

Rice bran cereal (rice bran puffed cereal) with the application of twin screw extrusion technology, could produce a crisp texture and crisp resistance time in milk almost the same as or longer than commercial breakfast cereal products (Budijanto et al., 2012). Food bar from a mixture of rice bran flour and corn flour (10:90), was able to replace food bars made from wheat flour with insignificant differences in nutritional quality (protein, fat, carbohydrates), and qualify as emergency food with a total energy of 232.43 kcal/50 g of the ingredient (Kusumastuty et al., 2015). Furthermore, extrusion products from a mixture of rice and rice bran were reported to contain sufficient nutritional value and had the potential to be developed into snack products (Hermanianto et al., 2000).

The introduction of rice bran as a functional food is important to do. One way is by highlighting its health benefits as a marketing strategy. Thus, it is hoped to open the community paradigm and increase interest in the downstream industry as an effort to develop functional food from rice bran.

Conclusion

The bioactive compounds in rice bran consist of several categories, such as phenolic acids, flavonoids, anthocyanins, and steroidal compounds. The mechanisms of the bioactive compound rice bran in preventing colon cancer was classified by its function as an antioxidant, damage of the lipid layer and mitochondrial membrane, activation of immune cells, modulation of the cell cycle, inhibition of protein invasion of tumor cells, metastases, and angiogenesis, and activation of protein caspase to encourage apoptosis. The development of rice bran itself as a functional food product in Indonesia is still on a laboratory scale, although some are developed into traditional foods. Educating the public about the benefits
of rice bran for health is a strategy for product development from rice bran raw material in the future.

References
Abdel-Aal, El-S.M., Young, J.C., & Rabalski, I., 2006. Anthocyanin Composition in Black, Blue, Pink, Purple, and Red Cereal Grains. *Journal of Agricultural and Food Chemistry*. 54(13): pp. 4696-4704. doi.org/10.1021/jf0606609

Aldudda, M., Islama, J., Shirakawa, H., Kosekib, T., Ardiansyah, & Komata, M., 2017. Rice Bran as a Functional Food: an Overview of the Conversion of Rice Bran into a Superfood/Functional Food: as an Overview of the Conversion of Rice Bran into a Superfood/Functional Food. London: IntechOpen.

Alonso-Castro, A.J., Dominguez, F., & Garcia-Carrancá, A., 2013. Rutin Exerts Antitumor Effects on Nude Mice Bearing SW480 Tumor. *Arch Med Res*. 44(5): pp. 346-351. doi.org/10.1016/j.arcmed.2013.06.002

Anand, P., Sundaram, C., Jhurani, S., Kunnumakkara, A.B., & Aggarwal, B.B., 2008. Curcumin and Cancer: An “Old-Age” Disease with an “Age Old” Solution. *Cancer Lett*. 267(1): pp. 133-164. doi.org/10.1016/j.canlet.2008.03.025

Anggraini, T., Novelina, Limber, U., & Amelia, R., 2015. Antioxidant Activities of Some Red, Black and White Rice Cultivar from West Sumatra, Indonesia. *Pak. J. Nutr*. 14(2): pp. 112-117. doi.org/10.3923/pjn.2015.112.117

Ardiansyah, Shirakawa, H., Koseki, T., Ohinata, K., Hashizume, K., & Komai, M., 2006. Rice Bran Fractions Improve Blood Pressure, Lipid Profile, and Glucose Metabolism in Stroke-Prone Spontaneously Hypertensive Rats. *J Agric Food Chem*. 54(5): pp. 1914-1920. doi.org/10.1021/jf0525611

Ashokkumar, P., & Sudhandiran, G., 2011. Luteolin Inhibits Cell Proliferation During Azoxymethane-Induced Experimental Colon Carcinogenesis Via Wnt/ß-Catenin Pathway. *Invest New Drugs*. 29(2): pp. 273-284. doi.org/10.1007/s10677-009-9359-9

Badan Pusat Statistik, 2018. *Luas Panen dan Produksi Beras di Indonesia 2018*. 2018.

Balaji, C., Muthukumaran, J., Vinothkumar, R., & Nalini, N., 2014. Anticancer Effects of Sinapic Acid on Human Colon Cancer Cell Lines HT-29 and SW480. *International Journal of Pharmaceutical & Biological Archives*. 5(3): pp. 176-183

Baskar, A.A., Ignacimuthu, S., Paulraj, G.M., & AlNumair, K.S., 2010. Chemopreventive Potential of beta-Sitosterol in Experimental Colon Cancer Model-an In Vivo and In Vivo Study. *BMC Complementary and Alternative Medicine*. 10(24): pp. 1-10. doi.org/10.1186/1472-6882-10-24

Bouzaie, N., Jaziri, S.K., Kovacic, H., Chekir-Ghedira, L., Ghedira, K., & Luis, J., 2015. The Effects of Caffeic, Coumaric and Ferulic Acid on Proliferation, Superoxide Production, Adhesion and Migration of Human Tumor In Vitro. *Eur J Pharmacol*. 766: pp. 799-105. doi.org/10.1016/j.ejphar.2015.09.044

Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R.L., Torre, L.A., & Jemal, A., 2018. Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *Ca Cancer J Clin*. 68(6): pp. 394-424. doi.org/10.3322/caac.21492

Budijanto, S., Sitanggang, A.Z., Wiaranti, H., & Koebiantero, B., 2012. Pengembangan Teknologi Sereal Sarapan Bekatul dengan Menggunakan Twin Screw Extruder. *J. Pascapanen*. 9(2): pp. 63-69. doi.org/10.21082/jpasca.v9n2.2012.63-69

Cai, H., Al-Fayez, M., Tunstall, R.G., Platton, S., Greaves, P., Steward, W.P., & Gescher, A.J., 2005. The Rice Bran Constituent Tricin Potently Inhibits Cyclooxygenase Enzymes and Interferes with Intestinal Carcinogenesis in ApcMin Mice. *Mol Cancer Ther*. 4(9): pp. 1287-1292. doi.org/10.1158/1535-7163.MCT-05-0165

Cempaka, L., Eliza, N., Ardiansyah, D.D., Handoko, & Astuti, R.M., 2018. Proximate composition, total phenolic content, and sensory analysis of rice bran tempe. *Makara Journal of Science*. 2018 Jun 6;22(2): pp. 89-94. doi.org/10.7454/mss.v22i2.9616

Cempaka, L., Casa, N., & Asiah, N., 2018. Chemical Composition and Sensory Analysis of Simulated Chips Based Rice Bran Tempe Flour. *Current Research in Nutrition and Food Science*. 6(3): pp. 826-34. doi.org/10.12944/CRNFSJ.6.3.25

Chiang, E.P., Tsai, S.Y., Kuo, Y.H., Pai, M.H., Chiu, H.L., Rodriguez, R.L., Tang, & Feng-Yao., 2014. Caffeic Acid Derivatives Inhibit The Growth of Colon Cancer: Involvement of The PI3-K/Akt and AMPK Signaling Pathways. *PLoS One*. 9(6): e99631. doi.org/10.1371/journal.pone.0099631

Cocacci, C., Bruno, A., Magnani, E., Bartolini, D., Principi, E., Dallaglio, K., Buccio, E.O., Finzi, G., Sesso, F., Noonan, D.M., & Albini, A., 2015. Effects of 5-Fluorouracil on Morphology, Cell Cycle, Proliferation,
Safrida, et al / Potency of Bioactive Compound of Rice Bran for Colon Cancer Prevention

Apoptosis, Autophagy and ROS Production in Endothelial Cells and Cardiomyocytes. PLoS One, 10(2):pp.1-25. doi: 10.1371/journal.pone.0115686

Garcia-Conesa, M.T., Wilson, P.D., Plumb, G.W., Ralph, J., & Williamson, G., 1999. Antioxidant Properties of 4,4′-Dihydroxy-3,3′-Dimethoxy-β,β′-Bicinnamic Acid (8,8-Diferulic Acid, Non-cyclic Form). J. Sci. Food Agric, 79(3):pp.379–384. doi:10.1002/(sici)1097-0010(19990301)79:3<379::aid-jfsa259>3.0.co;2-v

Ghasemzadeh, A., Karbalaii, M.T., Jaafar, H.Z.E., Ghasemzadeh, A., Karbalaii, M.T., Jaafar, H.Z.E., & Sharifi, Y., 2013. Effect of Elevated Carbon Dioxide (CO2) on Phenolic Acids, Flavonoids, Tocopherols, Tocotrienols, γ-Oryzanol (CO) on Phenolic Acids, Flavonoids, Tocopherols, Tocotrienols, γ-Oryzanol and Antioxidant Capacities of Rice (oryza sativa l.). J. Cereal Sci, 59(1):pp.15-24. doi.org/10.1016/j.jcres.2013.10.013

Guan, F., Li, G., Liu, A.B., Lee, M.J., Yang, Z., Chen, Y.K., Lin, Y., Shih, W., & Yang, C.S., 2012. δ- and γ-Tocopherols, but not α-Tocopherol, Inhibit Colon Carcinogenesis in Azoxymethane-Treated F344 Rats. Cancer Prev Res (Philad), 5(4):pp.644-654. doi:10.1158/1940-6207.CAPR-11-0521

Henderson, A.J., Ollila, C.A., Kumar, A., Borresen, E.C., Raina, K., Agarwal, R., & Ryan, E.P., 2012. Chemopreventive Properties of Dietary Rice Bran: Current Status and Future Prospects. Adv Nutr, 3(5):pp.643-653. doi:10.3945/an.112.002303

Hermanianto, J., Syarief, R., & Wulandari, Z., 2000. Analisis Sifat Fisikimia Produk Ekstrusi Hasil Samping Penggilingan Padi (Menir dan Bekatul). Bul. Teknol. dan Industri Pangan, 11(1):pp.5-10.

Hosoda, K., Sasahara, H., Matsushita, K., Tamura, Y., Miyaji, M., & Matsuyama, H., 2018. Anthocyanin and Proanthocyanidin Contents, Antioxidant Activity, and In Situ Degradability of Black and Red Rice Grains. Asian-Australas J Anim Sci, 31(8): pp.1213–1220. doi:10.5713/ajas.17.0655

Huang, Y.P., & Lai, H.M., 2016. Bioactive Compounds and Antioxidative Activity of Colored Rice Bran. Journal of Food and Drug Analysis, 24(3):pp.564-574. doi.org/10.1016/j.jfda.2016.01.004

Hui, C., Bin, Y., Xiaoping, Y., Long, Y., Chunye, C., Mantian, M., & Wenhua, L., 2010. Anticancer Activities of an Anthocyanin-Rich Extract From Black Rice Against Breast Cancer Cells In Vitro and In Vivo. Nutr Cancer, 62(8):pp.1128-1136. doi: 10.1080/01635581.2010.494821

[IARC] International Agency for Research on Cancer, 2018. Indonesia Source: Globocan 2018. The Global Cancer Observatory.

Islam, J., Koseki, T., Watanabe, K., Ardi, M., Tani, A., Ikawa, A., Alauddin, M., Goto, T., Aso, H., Komai, M., & Shirakawa, H., 2017. Dietary Supplementation of Fermented Rice Bran Effectively Alleviates Dextran Sodium Sulfate-Induced Colitis in Mice. Nutrients, 9(7):pp.747. doi:10.3390/nu9070747

Jaganathan, S.K., Supriyanto, E., & Mandal, M., 2013. Events Associated with Apoptotic Effect of p-Coumaric Acid in HCT-15 Colon Cancer Cells. World J Gastroenterol, 19(43):pp.7726-7734. doi:10.3748/wjg.v19.i43.7726

Janicke, B., Hermann, W., Hecker, M., & Oredsson, S.M., 2011. The Antiproliferative Effect of Dietary Fiber Phenolic Compounds Ferulic Acid and p-Coumaric Acid on the Cell Cycle of Caco-2 Cells. Nutr Cancer, 63(4):pp.611-622. doi.org/10.1080/01635581.2011.538486

Katayama, K., Ishii, T., Asai, T., Naitou, H., Maeda, N., Koizumi, F., Miyagawa, S., Ohashi, N., & Oku, N., 2010. Cancer Antineoangiogenic Therapy with Liposome Drug Delivery Systems Targeted to BiP/GRP78. Int J Cancer, 127(11):pp.2685-2698. doi:10.1002/ijc.25276

Kawakata, S., Yamamoto, T., Har, A., Shimizu, M., Yamada, Y., Matsunaga, K., Tanaka, T., & Mori, H., 2000. Modifying Effects of Ferulic Acid on Azoxymethane-Induced Colon Carcinogenesis in F344 Rats. Cancer Lett, 157(1):pp.15-21. doi:10.1016/s0304-
Phospholipids Composition of Whole Rice Bran After Solid-State Fungal Fermentation. 
*Bioresour Technol*, 102(17):pp.8335-8338. doi:10.1016/j.biortech.2011.06.025

Pandurangan, A.K., & Ganapasm, S., 2013. Luteolin Induces Apoptosis in Azoxymethane-Induced Colon Carcinogenesis Through Involvement of Bcl-2, Bax, and Caspase-3. *J Chem Pharm Res*, 5(4):pp.143-148.

Pandurangan, A.K., Dharmalingam, P., Ananda, SK, Ganapasm, S., 2014. Luteolin Inhibits Matrix Metalloproteinase 9 and 2 in Azoxymethane-Induced Colon Carcinogenesis in Mice. *Asian Pac J Cancer Prev*, 13(4):pp.1569-1573. doi:10.7314/apjcp.2012.13.4.1569

Pandurangan, A.K., Dharmalingam, P., Sadagopan, S.K., & Ganapasm, S., 2014. Luteolin Inhibits Matrix Metalloproteinase 9 and 2 in Azoxymethane-Induced Colon Carcinogenesis. *Hum Exp Toxicol*, 33(11):pp.1176-1185. doi:10.1177/0960327114522502

Pang, Y., Ahmed, S., Xu, Y., Beta, T., Zhu, Z., Shao, Y., & Bao, J., 2017. Bound Phenolic Compounds and Antioxidant Properties of Whole Grain and Bran of White, Red and Black Rice. *Food Chemistry*, 240:pp.212-221. doi.org/10.1016/j.foodchem.2017.07.095

Pavlou, S., Wang, L., Xu, H., & Chen, M., 2017. Higher Phagocytic Activity of Thioglycollate-Elicited Peritoneal Macrophages is Related to Metabolic Status of The Cells. *J Inflamm (Lond)*, 14(4):pp.1-6. doi:10.1186/s12950-017-0151-x

Poulev, A., Chen, M.H., Cherravuru, S., Raskin, I., & Belanger, F.C., 2017. Variation in Levels of The Flavone Tricin in Bran from Rice Genotypes Varying in Pericarp Color. *Journal of Cereal Science*, 79(7):pp.226-232. doi.org/10.1016/j.jcs.2017.11.001

Prasad, M.N.N., Sanjay, K.R., Khatokar, M.S., Vismaya, M.N., & Swamy, N., 2011. Health Benefits of Rice Bran - A Review. *J Nutr Food Sci*, 1(3):pp.1-7. doi:10.4172/2155-9600.1000108

Prasad, S., Gupta, S.C., Tyagi, A.K., & Aggarwal, B.B., 2016. γ-Tocotrienol Suppresses Growth And sensitises Human Colorectal Tumours to Capecitabine in A Nude Mouse Xenograft Model by Down-Regulating Multiple Molecules. *Br J Cancer*, 115(7):pp.814-824. doi:10.1038/bjc.2016.257

Pratiwi, R., & Purwesri, Y.A., 2017. Black Rice as A Functional Food in Indonesia. *Functional Foods in Health and Disease*, 7(3):pp.182-194. doi:10.31989/ffhd.v7i3.310

Ramos, A.A., Pereira-Wilson, C., & Collins, A.R., 2010. Protective Effects of Ursolic Acid and Luteolin Against Oxidative DNA Damage Include Enhancement of DNA Repair in Caco-2 Cells. *Mutat Res*, 692(1-2):pp.6-11. doi:10.1016/j.mrfmmm.2010.07.004

Rashid, N.Y.A., Razak, D.L.A., Jamaluddin, A., Sharifuddin, S.A., & Long, K., 2015. Bioactive Compounds and Antioxidant Activity of Rice Bran Fermented with Lactic Acid Bacteria. *Malaysian Journal of Microbiology*, 11(2):pp.156-162. doi:10.21161/mjm.12714

Rezaei, M., Zeidooni, L., Hashemitabar, M., Razazzadeh, S., Mahdavinia, M., & Ghasemi, K., 2014. Gamma-Tocopherol Enhances Apoptotic Effects of Lovastatin in Human Colorectal Carcinoma Cell Line (HT29). *Nutr Cancer*, 66(8):pp.1386-1393. doi:10.1080/01635581.2014.956250

Shafie, N.H., Mohd Es, N., Ikhin, H., Md, Akim, A., Saad, N., & Pandurangan, A.K., 2013. Preventive Inositol Hexaphosphate Extracted From Rice Bran Inhibits Colorectal Cancer Through Involvement of Wnt/-Catenein and COX-2 Pathways. *Biomed Res Int*, 2013:pp.1-10. doi:10.1155/2013/681027

Shao, Y., Xu, F., Sun, X., Bao, J., & Beta, T., 2014. Identification and Quantification of Phenolic Acids and Anthocyanins as Antioxidants in Bran, Ergo and Edosperm of White, Red and Black Rice Kernels (*Oryza sativa L.*). *Journal of Cereal Science*, 59(2):pp.211-218. doi.org/10.1016/j.jcs.2014.01.004

Sharma, S.H., Chellappan, D.R., Chinnaswamy, P., & Nagarajan, S., 2017. Protective Effect of p-Coumaric Acid Against 1,2 Dimethylhydrazine Induced Colonic Preneoplastic Lesions in Experimental Rats. *Biomed Pharmacother*, 94:pp.577-588. doi:10.1016/j.biopharma.2017.07.146

Sharma, S.H., Rajamanickam, V., & Nagarajan, S., 2018. Antiproliferative Effect of p-Coumaric Acid Targets UPR Activation By Downregulating Grp78 in Colon Cancer. *Chem Biol Interact*, 291:pp.16-28. doi:10.1016/j.cbi.2018.06.001

Subramanian, A.P., Jaganathan, S.K., Mandal, M., Supriyanto, E., & Muhamad, I., 2016. Gallic Acid Induced Apoptotic Events in HCT-15 Colon Cancer Cells. *World J Gastroenterol*, 22(15):pp.3952-3961. doi:10.3748/wjg.v22.i15.3952

Sumczynski, D., Kotásková, E., biková, H.D., & Mlček J., 2016. Determination of Contents...
and Antioxidant Activity of Free and Bound Phenolics Compounds and In Vitro Digestibility of Commercial Black and Red Rice (*Oryza sativa* L.) Varieties. *Food Chem.*, 211:pp.339-346. doi: 10.1016/j.foodchem.2016.05.081

Sun, Q., Spiegelman, D., Van, D.R.M., Holmes, M.D., Malik, V.S., Willett, W.C., & Hu, F.B., 2010. White Rice, Brown Rice, and Risk of Type 2 Diabetes in US Men and Women. *Arch Intern Med.*, 170(11):pp.961-969. doi: 10.1001/archinternmed.2010.109

Tuarita, M.Z., Sadek, N.F., Sukarno, Yuliana, N.D., & Budijanto, S., 2017 Pengembangan Bekatul sebagai Pangan Fungsional: Peluang, Hambatan, dan Tantangan. *Jurnal Pangan*, 26(2):pp.167-176.

Turktekin, M., Konac, E., Onen, H.I., Alp, E., Yilmaz, A., & Menevse, S., 2011. Evaluation of The Effects of The Flavonoid Apigenin on Apoptotic Pathway Gene Expression on The Colon Cancer Cell Line (HT29). *J Med Food*, 14(10):pp.1107-1117. doi: 10.1089/jmf.2010.0208

Um, M.Y., Ahn, J., & Ha, T.Y., 2013. Hypolipidaemic Effects of Cyanidin 3-Glucoside Rich Extract From Black Rice Through Regulating Hepatic Lipogenic Enzyme Activities. *J Sci Food Agric*, 93(12):pp.3126-3128. doi: 10.1002/jsfa.6070

Wang, W., VanAlstyne, P.C., Irons, K.A., Chen, S., Stewart, J.W., & Birt, D.F., 2004. Individual and Interactive Effects of Apigenin Analogs on G2/M Cell-Cycle Arrest in Human Colon Carcinoma Cell Lines. *Nutrition and Cancer*, 48(1):pp.106-114. doi: 10.1207/s15327914nc4801_14

Widowati, S., 2001. Pemanfaatan Hasil Samping Penggilingan Padi dalam menunjang Sistem Agroindustri di Pedesaan. *Bulletin AgroBio*, 4(1):pp.33-38.

Xia, X., Ling, W., Ma, J., Xia, M., Hou, M., Wang, Q., Zhu, H., & Tang, Z., 2006. an Anthocyanin-Rich Extract from Black Rice Enhances Atherosclerotic Plaque Stabilization in Apolipoprotein E–deficient Mice. *The Journal of Nutrition*, 136(8):pp.2220-2225.

Xu, M., Wang, S., Song, Y.U., Yao, J., Huang, K., & Zhu, X., 2016. Apigenin Suppresses Colorectal Cancer Cell Proliferation, Migration and Invasion Via Inhibition of The Wnt/β-Catenin Signaling Pathway. *Oncol Lett*, 11(5):pp.3075-3080. doi: 10.3892/ol.2016.4331

Xu, W., Du, M., Zhao, Y., Wang, Q., Sun, W., & Chen, B., 2012. γ-Tocotrienol Inhibits Cell Viability Through Suppression of β-Catenin/Tcf Signaling in Human Colon Carcinoma HT-29 Cells. *J Nutr Biochem*, 23(7):pp.800-807. doi:10.1016/j.jnutbio.2011.04.003

Yadav, R.K, Chae, Soo-Wan., Kim, Hyung-Ryong., & Chae, H.J., 2014 Endoplasmic Reticulum Stress and Cancer. *J Cancer Prev*, 19(2):pp.75–88. doi: 10.15430/JCP.2014.19.2.75

Younas, A., Bhatti, M.S., Ahmed, A., & Randhawa, M.A., 2011. Effect of Rice Bran Supplementation on Cookie Baking. *Pak. J. Agri. Sci*, 48(2):pp.129-134.

Zhang, J.S., Li, D.M., Ma, Y., Gu, Q., Wang, F.S., Jiang, S.Q., Chen, B.Q., & Liu, J.R. 2013. γ-Tocotrienol Induces Paraptosis-Like Cell Death in Human Colon Carcinoma SW620 Cells. *PLoS One*.E57779. doi.org/10.1371/journal.pone.0057779

Zheng, Q., Hirose, Y., Yoshih, N., Murakami, A., Koshimizu, K., Ohigashi, H., Sakata, K., Matsumoto, Y., Sayama, Y., & Mori, H., 2002. Further Investigation of The Modifying Effect of Various Chemopreventive Agents on Apoptosis and Cell Proliferation in Human Colon Carcinoma Cells. *J Cancer Res Clin Oncol*, 128(10):pp.539-546. doi: 10.1007/s00432-002-0373-y

Zulfafamy, K.E., Ardiansyah, & Budijanto, S., 2018. Antioxidative Properties and Cytotoxic Activity Against Colon Cancer Cell WiDr of *Rhizopus oryzae* and *Rhizopus oligosporus*-Fermented Black Rice Bran Extract. *Curr. Res. Nutr Food Sci Jour*, 6 (1) :pp.23-34. doi. org/10.12944/CRNFSJ.6.1.03