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Introduction

Rice bran, which consists of a combination of aleurone and pericarp, is the hard outer layer that is obtained during rice milling. Rice bran is rich in essential fatty acids and dietary fiber and contains proteins, dietary minerals, and vitamins.¹ Approximately 12–18.5% of rice bran is healthy oil, which contains 47% monounsaturated, 33% polyunsaturated, and 20% saturated fats as well as highly unsaponifiable ingredients including gamma-oryzanol, tocotrienols, and beta-sitosterol.² However, the high oil content of rice bran leads to easy rancidity by endogenous lipase, and stabilization is an effective way to avoid rancidification.³ Heat (dry or damp), microwave application, refrigeration, and proteasome treatment to inactivate endogenous lipase are useful methods to stabilize rice bran and mitigate its rancidification.^{3,4} The protein content comprises approximately 10–15% of rice bran, and it is increased to 18% in defatted rice bran.⁵ The protein content includes albumin (water soluble), globulin (salt soluble), prolamin (alcohol soluble), and glutelin (alkali soluble).⁶ The rice bran protein contains all the essential amino acids. Compared with that of rice protein, the amino acid composition of rice bran is closer to the recommended model of the Food and Agriculture

Organization (FAO)/World Health Organization (WHO), and its nutritional value is comparable to those of soybeans and egg proteins.⁷ Moreover, researchers are striving to isolate bioactive components from rice bran and reveal their functions.

Multiple isolation methods have been applied for the purification of rice bran fractions, and the method selection is based on the different physicochemical properties of the rice bran components. Rice bran oil (RBO) can be extracted using an aqueous method,⁸ an enzymatic method,⁹ and a screw press method.¹⁰ Subsequently, modified methods such as ultrasound and microwave-assisted aqueous extraction of RBO have been used.^{11,12} Rice bran protein (RBP) can be extracted using an alkali solution,¹³ enzymatic,¹⁴ or physical method.¹⁵ With the development of the extraction technology, the yield and purity of the rice bran components will be further improved.

Fermentation is an important method for the deep processing of rice bran; thus, the fermentation products can be used as high-quality feed¹⁶ and raw materials for food and beverage production.¹⁷ The traditional zymogenous microorganisms include yeast, *Aspergillus oryzae*, lactic acid bacteria, and *Lentinus edodes*.^{18–21} Fermentation contributes to an increased amino acid content and a decreased fatty acid content.²² Moreover, the bioactive components obtained from fermented rice bran (FRB) exert various biological activities (Table 1).

With the development of nutraceuticals, researchers and consumers are currently paying increasing interest to the possible preventive/therapeutic effects of rice bran on pathological conditions;^{24–27} nutraceuticals have attracted significant attention due to their abilities to regulate the

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Table 1 Rice bran fermentation and function

Raw material	Type of fermentation microorganism	Model	Function	Reference
Brown rice and rice bran	<i>Aspergillus oryzae</i>	Mice bearing tumors derived from QR-32 cells, ApcMin/+ mice, female A/J mice, male F344 rats, or female LEC rats	Fermented brown rice and rice bran administration reduced the expression of the inflammation-related genes TNF- α , Mac-1, CCL3 and CXCL2 in tumor-bearing mice; suppressed the multiplicity of colon tumors in ApcMin/+ mice exposed to dextran sodium sulfate; inhibited NNK-induced lung tumorigenesis and NMBA-induced esophageal tumorigenesis; protected against the development of hepatitis; and suppressed diethylnitrosoamine (DEN)- and phenobarbital (PB)-induced hepatocarcinogenesis	22,34-38
Rice bran	Fungi and lactic acid bacteria	Colitis in mice	Dietary supplementation with fermented rice bran attenuated dextran sodium sulfate-induced intestinal inflammation <i>via</i> elevating short-chain fatty acids and tryptamine production	19
Rice bran along with <i>Angelicae gigantis</i> , <i>Cnidium officinale</i> , <i>Artemisia princeps</i> , and <i>Camellia sinensis</i>	<i>Lactobacillus rhamnosus</i> and <i>Pichia deserticola</i>	Atopic dermatitis in mice	Fermented rice bran combined with <i>Angelicae gigantis</i> , <i>Cnidium officinale</i> , <i>Artemisia princeps</i> , and <i>Camellia sinensis</i> mitigated 1-chloro-2,4-dinitrobenzene-induced atopic dermatitis through inhibiting the expression of cytokines and Cox-2	1
Rice bran	<i>Lentinus edodes</i>	Healthy participants	Supplementation with fermented rice bran significantly increased IFN- γ secretion without causing obvious adverse effects and with no significant effects on the production of IL-2, IL-4, IL-10, IL-12, or TNF- α	21
Rice bran	<i>Issatchenka orientalis</i> MFST1	3T3-L1 adipocytes	Fermented rice bran treatment reduced reactive oxygen species generation and oxidative stress-induced insulin resistance	39
Neptune rice bran	<i>Saccharomyces boulardii</i>	Raji B lymphomas	Treatment with fermented Neptune rice bran extracts significantly inhibited the viability of Raji B lymphomas	23
Rice bran	<i>Lactobacillus rhamnosus</i> and <i>Saccharomyces cerevisiae</i>	B16F1 melanoma	Fermented rice bran extracts reduced the expression of microphthalmia-associated transcription factor and inhibited the melanogenesis of B16F1 melanoma cells	20
Rice bran	<i>Saccharomyces cerevisiae</i>	Rats or mice	Oral administration of fermented rice bran induced an anti-stress and anti-fatigue response	40



immune response, glucose and lipid metabolism. Black rice bran, which is rich in gamma-oryzanol, could promote the expression of CD14 and toll-like receptor 4 and enhance the phagocytic activity of the macrophages RAW264.7.²⁸ The extracts, such as phenolic, flavonoid, anthocyanin, and proanthocyanidin extracts, obtained from rice bran inhibit alpha-glucosidase activity and promote glucose uptake in 3T3-L1 adipocytes, which are critical factors for glucose homeostasis.²⁹ Monacolins (present in large amounts in red yeast rice, which is produced by the fermentation of *Monascus purpureus* mold) have been shown to be bioactive for cholesterol reduction.³⁰

Studies have demonstrated that rice bran extracts and FRB serve critical roles in the regulation of oxidative response, inflammatory reaction, immune function, cholesterol metabolism, and tumor suppression.^{31–33} In this study, we emphasized the potential function of rice bran extracts and FRB in cancer prevention and therapy.

Anti-cancer activity: mechanism of action and chemopreventive effects

Reducing inflammatory reaction

Inflammation is an important inducer of tumor progression, and many cancers arise from infection and inflammation.⁴¹

Inflammation also aids in cancer cell proliferation and promotes angiogenesis and cell mobility.⁴² Thus, reducing inflammation is a promising therapeutic target for treating cancer.⁴³ Recent data demonstrate that rice bran extracts and FRB are helpful in attenuating inflammation (Fig. 1). A high-fat diet results in chronic intestinal inflammation,⁴⁴ and rice bran enzymatic extract supplements mitigate high-fat diet-induced inflammatory factor secretion.⁴⁵ The rice bran protein hydrolysate also contributes to the suppression of proinflammatory cytokine expression in rats fed a high-carbohydrate, high-fat diet.⁴⁶ RBO also exerts an anti-inflammatory response and can reduce the inflammatory response of rats fed partially hydrogenated vegetable fat.⁴⁷ A subsequent study has shown that the gamma-oryzanol component of RBO serves an essential role in the anti-inflammatory activity.⁴⁸ Gamma-tocotrienol is another important component of rice bran extracts that represses pancreatic tumor growth by reducing the NF-κB-mediated inflammatory microenvironment.⁴⁹ The colitis effect is a critical inducer of colon cancer,⁵⁰ and a dietary supplement of FRB effectively inhibits dextran sodium sulfate-induced colitis *via* reducing inflammatory cell infiltration and inflammatory cytokine production.¹⁹ Overall, the rice bran extracts and FRB might serve essential roles in preventing cancer development *via* downregulation of the inflammatory reaction.

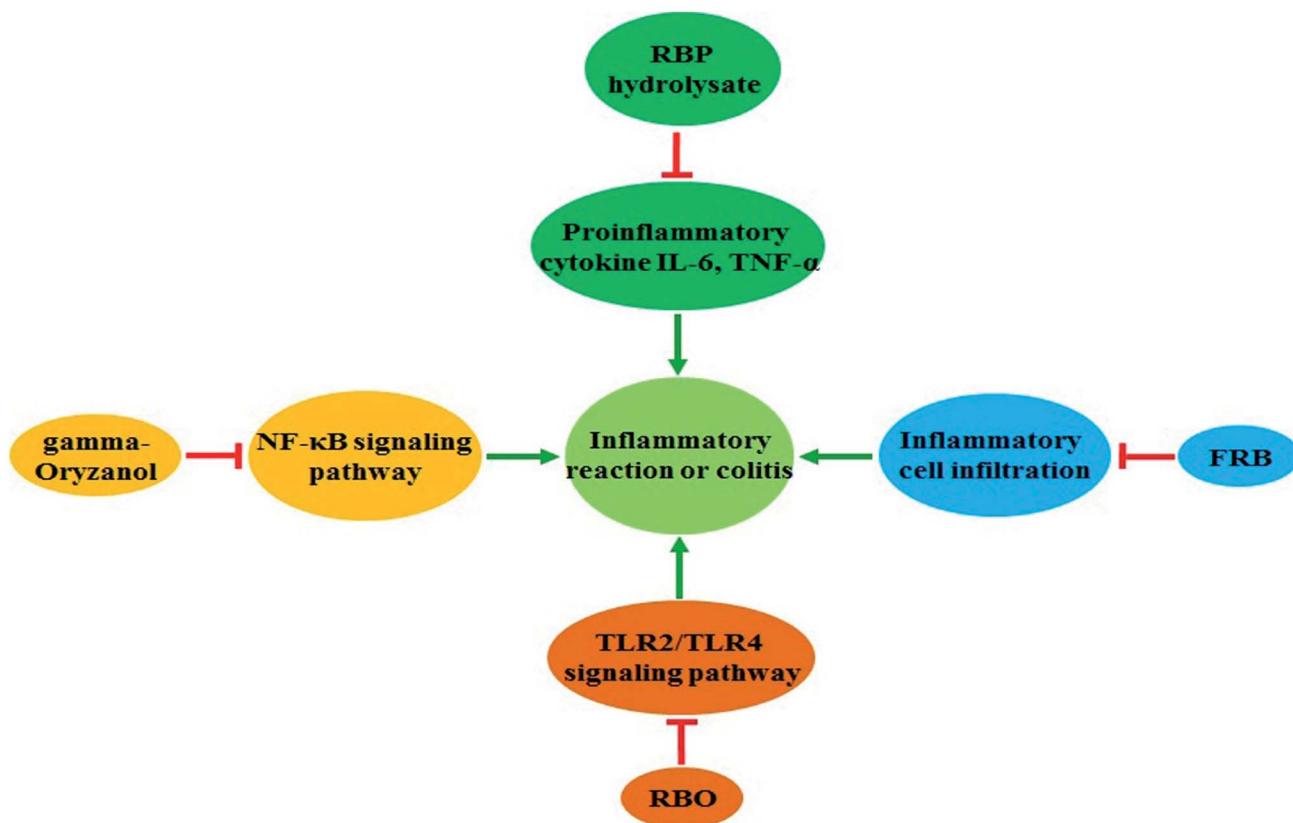


Fig. 1 The role of rice bran extracts and FRB in reducing inflammation. Supplementation of RBP hydrolysate and RBO inhibited the production of proinflammatory factors. Gamma-oryzanol inactivated the NF-κB signaling pathway and reduced inflammatory reactions. FRB effectively mitigated dextran sodium sulfate-induced colitis by suppressing the infiltration of inflammatory cells and the secretion of inflammatory factors.



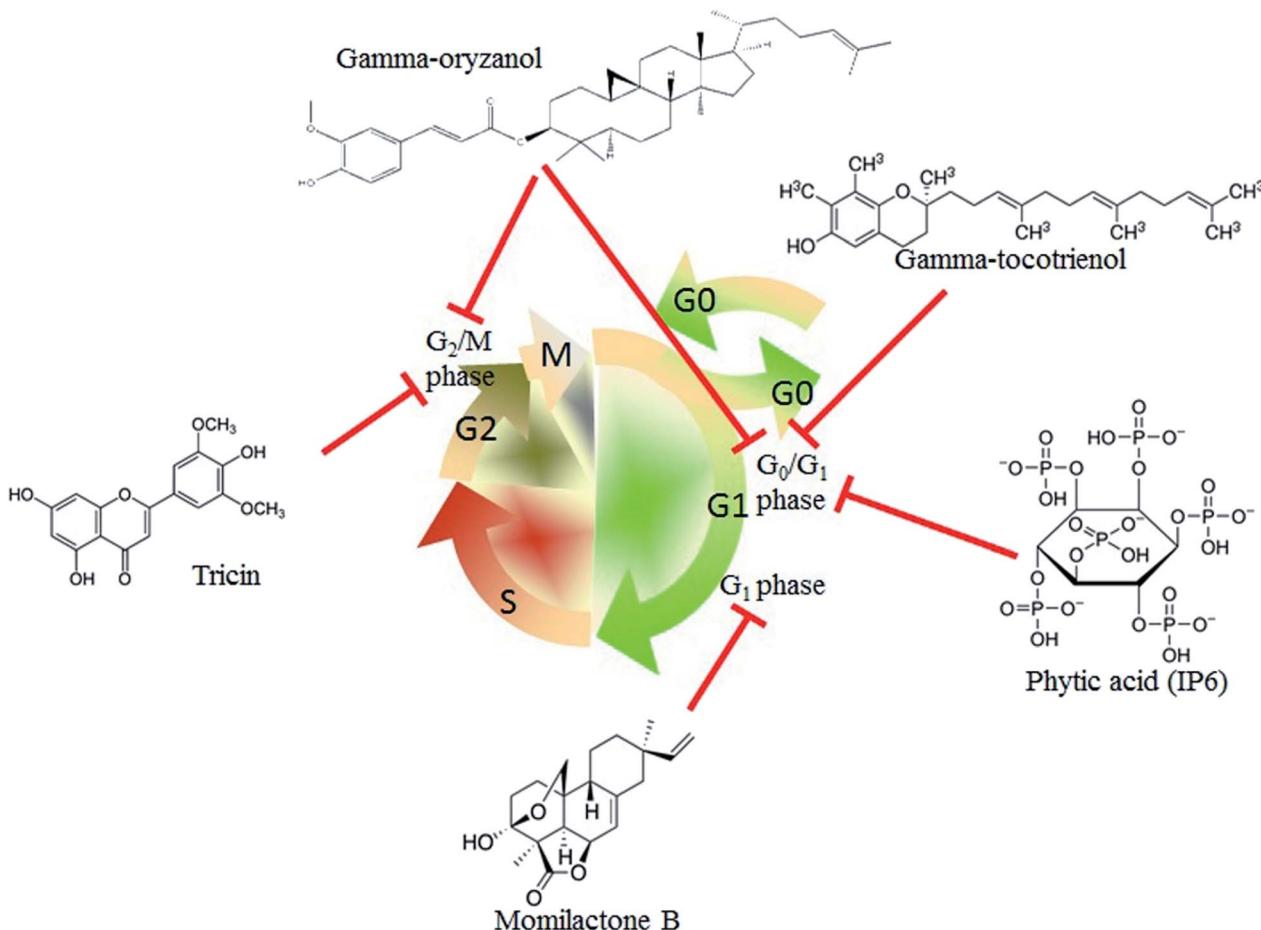


Fig. 2 Rice bran extracts arrest the cancer cell cycle. Gamma-tocotrienol, gamma-oryzanol, and phytic acid (IP6) arrested the cell cycle at the G0/G1 phase of gastric adenocarcinoma SGC-7901 cells; prostate cells DU145, colon cancer cells HT-29, and breast cancer cells MCF-7. Momilactone B treatment resulted in human leukemia cell U937 arrest at the G1 phase. Tricin and gamma-oryzanol could also arrest the breast cancer cells MDA-MB-468 and prostate cell lines (PC3 and LNCaP) at the G2/M phase.

Cell cycle arrest

Aberrant cell cycle protein expression leads to uncontrolled cell proliferation, which is one of the critical factors for cancer occurrence.⁵¹ Cell cycle blockers are ideal targets for cancer therapy.⁵² As shown in Fig. 2, tricin is an important flavone component of rice bran. A study has indicated that tricin arrests the human malignant breast cancer cell line MDA-MB-468 at the G2/M phase. Furthermore, the volume of tumors is significantly decreased in nude mice implanted with tricin-pretreated MDA-MB-468 cells as compared to that in the control group.⁵³ Thus, tricin treatment results in arrest of the cancer cell cycle and inhibition of the tumor growth. Gamma-tocotrienol also inhibits human gastric adenocarcinoma SGC-7901 cell proliferation *via* arresting the cell cycle at the G0/G1 phase.⁵⁴ Momilactone B, a terpenoid phytoalexin derived from rice bran, exerts its anti-cancer effect by arresting the human leukemia U937 cells at the G1 phase.⁵⁵ Gamma-oryzanol can arrest the cell cycle of the prostate cell lines PC3 and LNCaP (at the G2/M phase) and DU145 (at the G0/G1 phase).⁵⁶ Phytic acid, which is also known as inositol hexakisphosphate (IP6), is a bioactive compound existing in rice bran, and it induces cell cycle arrest at the G0/G1 phase of the human colon cancer cell line HT-29

and breast cancer cell line MCF-7.^{57,58} In summary, rice bran extracts play an important role in suppressing cancer cell proliferation by blocking cell cycle progression.

Promoting cell apoptosis

Dysregulation of cell apoptosis is one of the vital aspects of cancer development. Promotion of cancer cell apoptosis serves a critical role in cancer prevention and therapy. Moreover, rice bran extracts and FRB exhibit a role in regulating cancer cell apoptosis. Water-based extracts of rice bran dramatically induce colon cancer cell apoptosis.⁵⁹ Phytic acid from rice bran elicits a proapoptotic effect on the colon cancer cells HT-29 through the regulation of Bax and Bcl-xL protein expression.⁶⁰ Moreover, phytic acid induces the apoptosis of the liver cancer cells HepG2 by upregulating the expression of the proapoptotic genes p53 and Bax and downregulating the expression of the antiapoptotic gene Bcl-2.⁶¹ Cycloartenyl ferulate, one of the phenolic compounds from rice bran, promotes the activity of the death receptors DR4 and DR5, suppresses the antiapoptotic Bcl-2 expression, elevates the proapoptotic Bak expression, and leads to the apoptosis of the colon cancer cells SW480.⁶² Tocotrienol is

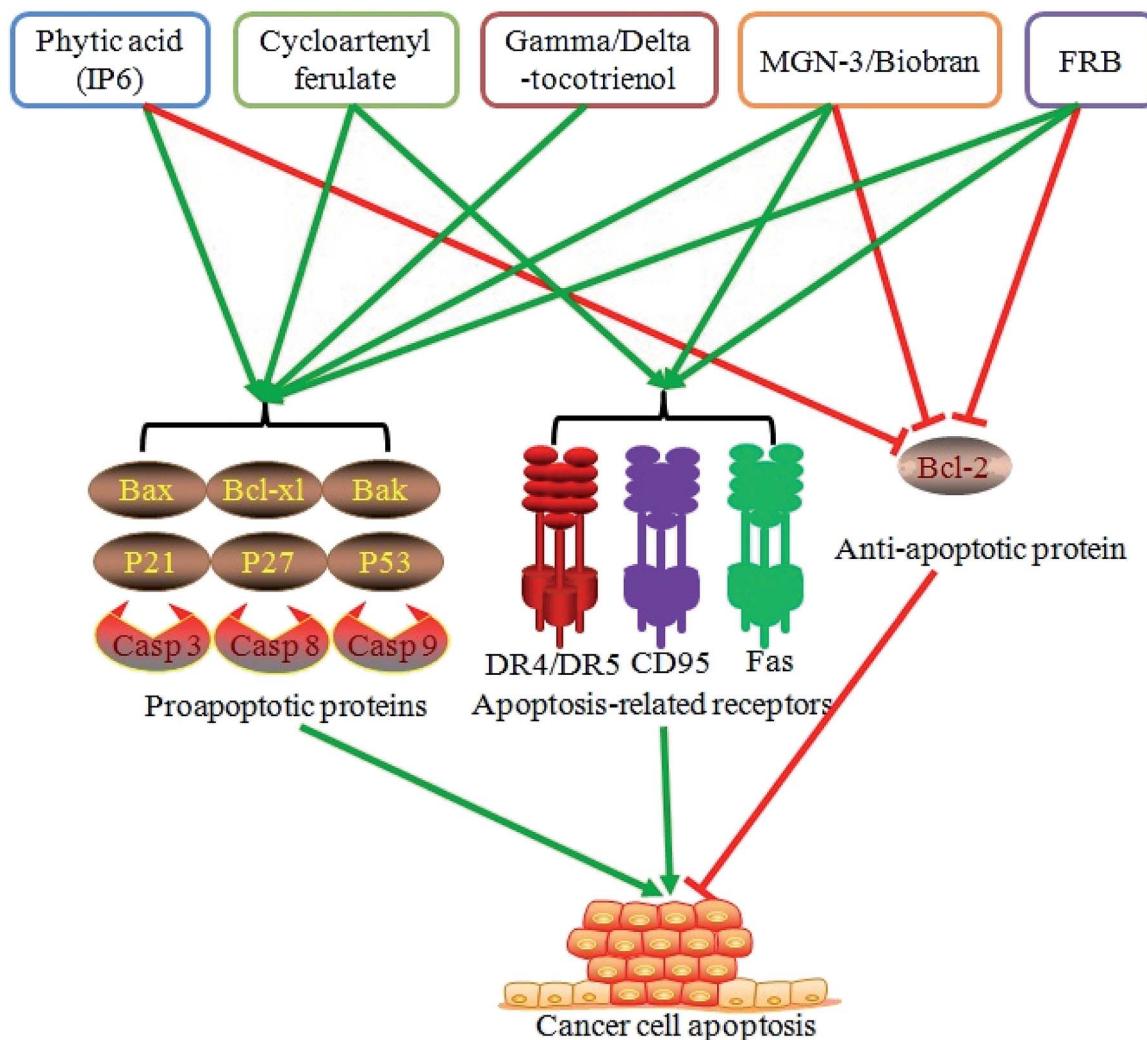


Fig. 3 Rice bran extracts and FRB promote cancer cell apoptosis. Rice bran extracts (phytic acid, cycloartenyl ferulate, gamma/delta-tocotrienol, and MGN-3/Biobran) and FRB administration dramatically induced cancer cell apoptosis via promoting the expression of proapoptosis proteins (Bax, Bcl-xL, Bak, P21, P27, P53, and caspase 3/8/9), activating apoptosis-related receptors (DR4/5, CD95, and Fas) or inhibiting the expression of the anti-apoptotic protein Bcl-2.

also involved in mediating cancer cell apoptosis. Gamma-tocotrienol induces caspase 3 activation and contributes to the apoptosis of the gastric adenocarcinoma SGC-7901 cells,⁵⁴ whereas delta-tocotrienol elevates the expression of p21, p27, and caspases 3 and 9, represses Akt phosphorylation, and results in human colorectal adenocarcinoma DLD-1 cell apoptosis.⁶³ Administration of MGN-3/Biobran, a modified arabinoxylan rice bran, can promote tumor cell apoptosis and reduce tumor volume and weight in mice bearing a solid Ehrlich carcinoma.⁶⁴ MGN-3/Biobran also enhances yeast-induced breast cancer cell apoptosis via activating the caspases 8 and 9 in the MCF-7 cells and caspases 3, 8, and 9 in the HCC70 cells.⁶⁵ Other studies indicate that MGN-3/Biobran exhibits a proapoptotic effect on the human leukemic HUT78 cells in a death receptor CD95-dependent manner⁶⁶ and induces the human multiple myeloma cell line U266 cell apoptosis by decreasing the Bcl-2 expression and increasing the Bax expression.⁶⁷ A recent study has also showed that FRB with *Aspergillus oryzae*

activates the expression of the death receptor DR5 and Fas protein, promotes the protein levels of caspases 3, 8, and 9, reduces the Bcl-2 expression, and leads to the human acute lymphoblastic leukemia Jurkat cell apoptosis.⁶⁸ In general, rice bran extracts and FRB might promote cancer cell apoptosis by enhancing the proapoptotic protein expression and repressing the antiapoptotic protein expression (Fig. 3).

Enhancing the chemopreventive effects

Chemoprevention is the use of natural or synthetic agents to inhibit, delay, or reverse carcinogenesis.⁶⁹ As shown in Fig. 4, studies have demonstrated that rice bran extracts and FRB can be effective natural agents for chemoprevention. Diethylnitrosamine (DEN) and 2-acetylaminofluorene (AAF) are carcinogens that can induce the development of liver cancer. An *in vivo* study has indicated that DEN/AAF exposure elevates hepatic lipid peroxidation and low-density lipoprotein oxidation and leads to liver carcinogenesis in Sprague-Dawley rats.⁷⁰ However,



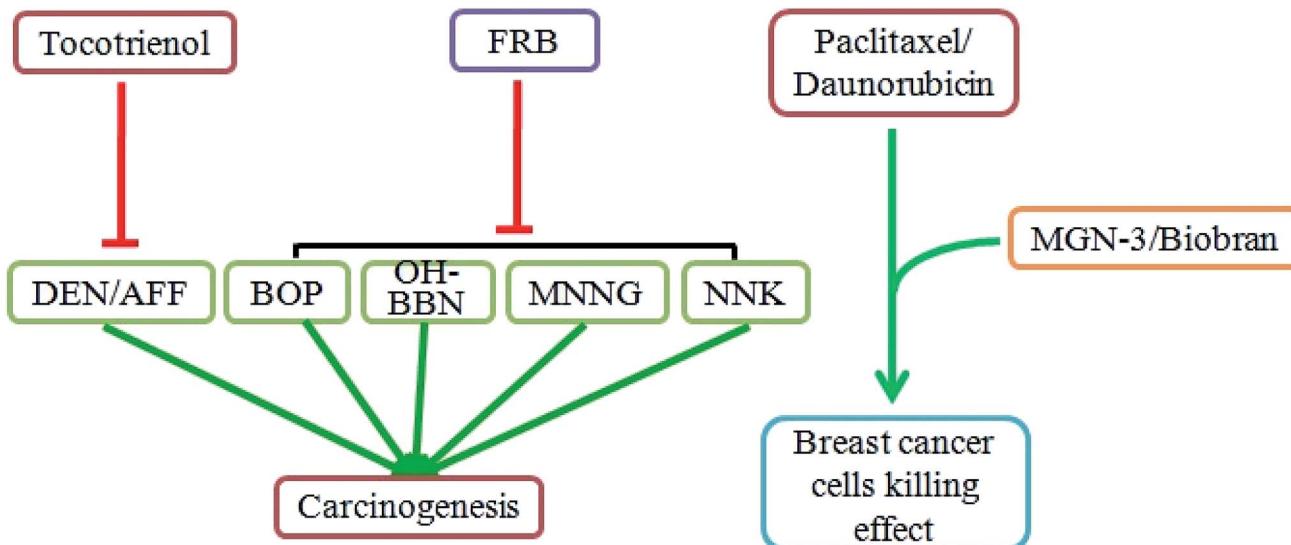


Fig. 4 Rice bran extracts and FRB have chemopreventive effects. Tocotrienol treatment reduced DEN/AFF-induced liver carcinogenesis. A diet of FRB effectively inhibited BOP-induced pancreatic cancer, OH-BBN-induced bladder cancer, MNNG-induced gastric cancer, and NNK-induced lung cancer. MGN-3/Biobran supplementation enhanced the susceptibility of breast cancer cells to paclitaxel and daunorubicin.

treatment with tocotrienol-rich fraction reduced the DEN/AFF-induced activation of the abovementioned parameters and hepatocarcinogenesis.⁷⁰ The total phenolics and gamma-tocotrienol in rice bran have a positive correlation with reduced colorectal cancer cell growth.⁷¹ *N*-Nitrosobis(2-oxopropyl)amine (BOP), *N*-butyl-*N*-(4-hydroxybutyl)-nitrosamine (OH-BBN), *N*-methyl-*N*¹-nitro-*N*-nitrosoguanidine (MNNG) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) are well-known carcinogens. Diets with 5% or 10% fermented brown rice and rice bran have significantly inhibited BOP-induced pancreatic cancer,⁷² OH-BBN-induced bladder carcinogenesis,⁷³ MNNG-induced gastric cancer,⁷⁴ NNK-induced lung cancer,³⁵ and prostate carcinogenesis in the transgenic rat adenocarcinoma of the prostate (TRAP) strain.⁷⁵

In addition to directly reducing chemical-induced carcinogenesis, the rice bran extracts can enhance the sensitivity of cancer cells to chemotherapy drugs. MGN-3/Biobran treatment significantly increases the susceptibility of the human non-metastatic breast cancer cells MCF-7 and metastatic murine breast cancer cells 4T1 to paclitaxel.⁷⁶ Another study showed that MGN-3/Biobran contributes to enhanced sensitivity of the breast cancer cells MCF-7 and HCC-70 to daunorubicin.⁷⁷ Overall, rice bran extracts and FRB are potential chemopreventive agents that act by reducing carcinogen-related cancer induction and enhancing the susceptibility of cancer cells to chemotherapy drugs (Fig. 4).

Clinical trials

In addition to studies that have focused on the function of rice bran extracts and FRB in cell or animal models, increasing research is being concentrated on their clinical effects. Dietary supplementation of rice bran dramatically downregulates the level of the inflammatory factor IL-6 in overweight and obese adults.⁷⁸ In patients with type II diabetes, the dietary

consumption of rice bran oil significantly reduces the blood levels of total cholesterol, triglyceride, and low-density lipoprotein cholesterol.^{79,80} In addition, RBO containing gamma-oryzanol⁸¹ or rice bran extract containing an acylated steryl glucoside fraction⁸² effectively decreases low-density lipoprotein cholesterol levels. Thus, rice bran administration could mitigate the inflammatory reaction and reduce the level of blood lipids in obese and hyperlipidemic subjects. Rice bran extracts still play a crucial role in regulating innate immune activity. MGN-3/Biobran consumption for 30 days dramatically increased the NK cell activity in geriatric subjects (over 65 years old).⁸³ A study that enrolled patients with multiple myeloma has also indicated that dietary supplementation with MGN-3/Biobran contributes to elevated NK cell activity.⁸⁴ The function of activated NK cells is to help recognize and kill cancer cells, which is critical for cancer prevention and immunotherapy. Another clinical effect of rice bran extracts is the regulation of gastrointestinal function. Administration of MGN-3/Biobran remarkably attenuates the clinical symptoms of patients with diarrhea-predominant or mixed-type irritable bowel syndrome.⁸⁵ A heat-stabilized rice bran diet offers the benefits of bacterial richness and diversity in the gut, helps with microbial metabolism, modulates stool metabolite profiles, and contributes to chemoprevention in colorectal cancer survivors.⁸⁶⁻⁸⁸ The function of rice bran in altering gut microbiota might contribute to the relief of adverse gastrointestinal effects in cancer patients during chemotherapy. A study that enrolled patients with cervical cancer indicated that the oral intake of hydrolyzed rice bran effectively attenuated the diarrheal side effects of chemotherapy.⁸⁹ Rice bran extracts also exert an adjuvant therapeutic effect on cancer patients. A study of hepatocellular carcinoma patients receiving interventional therapy demonstrated that dietary supplementation of MGN-3/Biobran significantly decreased the recurrence and increased the two-year survival rate.⁹⁰ Therefore, rice bran extracts play



Table 2 Detailed information of rice bran extracts in clinical trials

Types of extract	Types of trial	Registration number	Target enroll number	Disease type	Conclusion	Reference
Rice husk powder or rice bran	Randomized trial	IRCT2015040721652N1	105	Overweight and obese adults	Rice husk powder and rice bran consumption combined with an energy-restricted diet significantly reduced the levels of inflammatory factor IL-6 in overweight and obese subjects	78
Rice bran oil (RBO) or canola oil (CO)	Randomized, controlled, parallel-group trial	IRCT2014050417568N1	75	Postmenopausal women with type 2 mellitus	RBO or CO treatment attenuated lipid disorders in type 2 diabetic women. RBO improved the lipid profile more efficiently than CO	79
Rice bran and sesame blend oil	Open-label randomized trial		300	Patients with type 2 mellitus	A novel blend of 20% cold-pressed unrefined sesame oil and 80% physically refined rice bran oil, when used as cooking oil, lowered hyperglycemia and improved the lipid profile in type 2 diabetes mellitus patients	80
Rice bran oil (RBO) containing gamma-oryzanol	Randomized, double-blind, controlled trial		59	Hyperlipidemic subjects	RBO with gamma-oryzanol decreased LDL-C levels and increased the antioxidant capacity in hyperlipidemic subjects. Thus, RBO consumption may reduce cardiovascular disease risk factors	81
Rice bran extract containing acylated steryl glucoside fraction (RB-ASG)	Randomized, double-blinded trial		51	Obese men	RB-ASG fraction might reduce the blood LDL cholesterol levels and the risk of arteriosclerosis in obese Japanese men	82
MGN-3/Biobran	Randomized, double-blind, placebo-controlled trial		12	Healthy geriatric subjects	Biobran/MGN-3 induced a significant increase in NK activity, which may increase resistance to viral infections and cancers in the geriatric population	83
MGN-3/Biobran	Randomized, placebo-controlled trial		48	Multiple myeloma patients	MGN-3 might represent an immunologically relevant product for activating innate immunity in multiple myeloma patients and warrants further testing to demonstrate clinical efficacy	84
MGN-3/Biobran	Pilot, randomized, controlled trial		40	Diarrhea-predominant or mixed-type irritable bowel syndrome	The administration of Biobran/MGN-3 improved IBS symptoms. The anti-inflammatory and/or immune modulatory effects of Biobran might be useful in IBS patients	85
Heat-stabilized rice bran or cooked navy bean powder	Randomized-controlled pilot trial	NCT01929122	29	Colorectal cancer survivors	Dietary supplementation of heat-stabilized rice bran or cooked navy bean powder had benefits for gut microbiotic richness and microbial metabolism	86
Heat-stabilized rice bran	Randomized controlled trial	NCT01929122	29	Colorectal cancer survivors	Heat-stabilized rice bran consumption favorably modulated the stool metabolome of colorectal cancer survivors	87
Heat-stabilized rice bran or cooked navy bean powder	Randomized controlled trial	NCT01929122	29	Colorectal cancer survivors	Increased dietary heat-stabilized rice bran or cooked navy bean powder consumption contributed to colorectal cancer chemoprevention	88
Hydrolyzed rice bran	Randomized, double-blind pilot trial	UMIN000004350	20	Cervical cancer patients	Hydrolyzed rice bran administration may relieve diarrhea, an acute-phase gastrointestinal side effect of chemoradiotherapy	89
MGN-3/Biobran	Three-year randomized trial	NCT01018381	68	Patients with hepatocellular carcinoma	Biobran/MGN-3, in conjunction with intervention therapy, may be useful for the treatment of hepatocellular carcinoma; this treatment showed lower recurrence and an increased the two-year survival rate	90



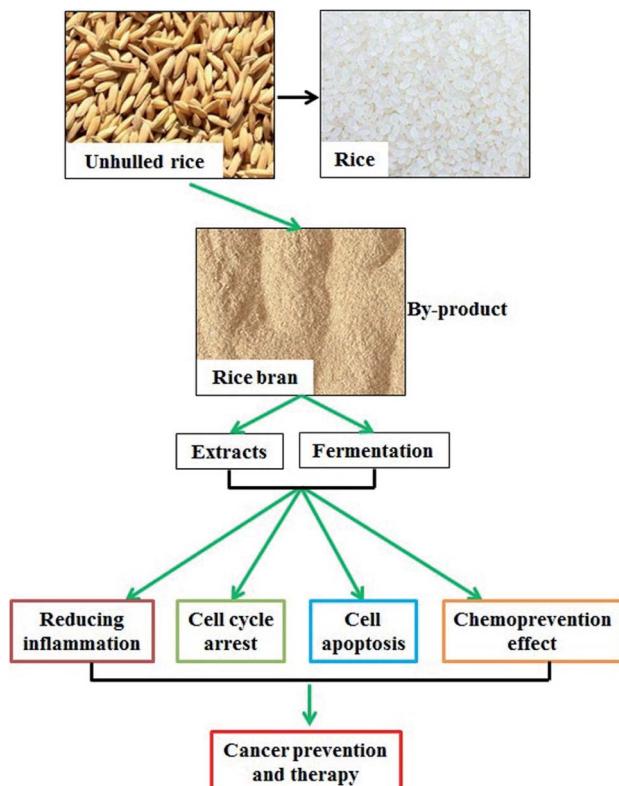


Fig. 5 The potential mechanism of treatment with rice bran extracts and fermented products for cancer prevention and therapy. Rice bran is a by-product during rice processing, and the bioactive components of rice bran extracts and fermented products exert important roles in cancer prevention and therapy. Administration of these bioactive components contributes to reducing inflammatory reactions, arresting the cell cycle, promoting cell apoptosis, and preventing cancer occurrence.

a large role in regulating inflammation, lipid metabolism, and clinical cancer therapy *via* the modulation of gastrointestinal function, chemotherapy effects, and interventional therapy effects (Table 2).

Conclusion

Rice bran extracts and FRB are promising adjuvant therapeutic agents for cancer prevention and therapy. They might play a critical role in suppressing local inflammation, arresting the cancer cell cycle, promoting cancer cell apoptosis, and enhancing the chemopreventive effects (Fig. 5). Furthermore, the benefits of dietary supplementation of rice bran include modulation of the microbiota richness of the gut, maintenance of the gastrointestinal function, attenuation of the side effects and enhancement of the therapeutic effects in cancer patients. In general, as potential nutraceuticals, rice bran extracts and fermentation products are greatly expected to contribute health benefits to those suffering from pathological conditions. Furthermore, nutraceutical supplementation is a new clinically auxiliary strategy for the prevention or therapeutic treatment of acute and chronic diseases.

Conflicts of interest

The authors declare no conflict of interest.

Abbreviations

RBO	Rice bran oil
RBP	Rice bran protein
FRB	Fermented rice bran
DR	Death receptor
Bcl-2	B-cell lymphoma-2
Bax	BCL2-associated X protein
Bak	Bcl-2 homologous antagonist/killer
Bcl-xL	B-cell lymphoma-extra large
MGN-3/	Arabinoxylan rice bran
Biobran	
DEN	Diethylnitrosamine
AAF	2-Acetylaminofluorene
BOP	N-Nitrosobis(2-oxopropyl) amine
OH-BBN	N-Butyl-N-(4-hydroxybutyl)-nitrosamine
MNNG	N-Methyl-N'-nitro-N-nitrosoguanidine
NNK	4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone
CD95	Cluster of differentiation 95
IL	Interleukin
NK	Natural killer
TNF	Tumor necrosis factor
Mac-1	Macrophage-1
CCL	Chemokine (C-C motif) ligand
CXCL	Chemokine (C-X-C motif) ligand
LDL	Low-density lipoprotein

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Notes and references

- 1 H. Y. Shin, S. M. Kim, J. H. Lee and S. T. Lim, *Food Chem.*, 2019, **272**, 235–241.
- 2 S. Bhosale, *Curr. Res. Nutr. Food Sci.*, 2015, **3**, 74–80.
- 3 D. Saikia and S. C. Deka, *Int. Food Res. J.*, 2011, **18**, 21–30.
- 4 W. A. D. V. Weerathilake, S. S. E. Ranawana, N. R. Abeynayake, A. N. F. Perera and W. M. M. P. Wijeratne, 2012.
- 5 T. Laokulidilok and Y. Rattanathanan, *Cereal Chem.*, 2014, **91**, 560–565.

6 C. Fabian and Y. H. Ju, *Crit. Rev. Food Sci. Nutr.*, 2011, **51**, 816–827.

7 J. S. Hamada, *J. Food Sci.*, 2000, **65**, 305–310.

8 S. W. Han, K. M. Chee and S. J. Cho, *Food Chem.*, 2015, **172**, 766–769.

9 B. Amarasinghe, M. P. M. Kumarasiri and N. C. Gangodavilage, *Food Bioprod. Process.*, 2009, **87**, 108–114.

10 P. Hanmoungjai, D. L. Pyle and K. Niranjan, *J. Am. Oil Chem. Soc.*, 2001, **78**, 817–821.

11 S. Sayasoothorn, S. Kaewrueng and P. P. A. T. T. A. Ul, *Rice Science*, 2012, **1**, 75–78.

12 M. Khoei and F. Chekin, *Food Chem.*, 2016, **194**, 503–507.

13 M. A. Chao, Y. J. Liao, T. Yang, H. R. Zou, W. U. Yao and D. J. Wan, *Food Sci. Technol.*, 2014, **39**, 132–135.

14 R. Gnanasambandam and N. S. Hettiarachchy, *J. Food Sci.*, 1995, **60**, 1066–1069.

15 M. V. Grossman, C. S. Rao and R. S. F. Da silva, *Journal of Food Biochemistry*, 1980, **4**, 181–188.

16 X. U. Feng and C. Y. Wang, *Food Sci.*, 2014, **35**, 11–16.

17 A. K. K San Mu, A. Ideris and C. R. Saad, *J. Anim. Vet. Adv.*, 2011, **10**, 2990–2995.

18 L. Liu, R. Zhang, Y. Deng, Y. Zhang, J. Xiao, F. Huang, W. Wen and M. Zhang, *Food Chem.*, 2017, **221**, 636–643.

19 J. Islam, T. Koseki, K. Watanabe, S. Budijanto, A. Oikawa, M. Alauddin, T. Goto, H. Aso, M. Komai and H. Shirakawa, *Nutrients*, 2017, **9**, E747.

20 S. Y. Chung, Y. K. Seo, J. M. Park, M. J. Seo, J. K. Park, J. W. Kim and C. S. Park, *Biosci., Biotechnol., Biochem.*, 2009, **73**, 1704–1710.

21 J. Y. Choi, D. J. Paik, D. Y. Kwon and Y. Park, *Nutr. J.*, 2014, **13**, 35.

22 K. Onuma, Y. Kanda, S. Suzuki Ikeda, R. Sakaki, T. Nonomura, M. Kobayashi, M. Osaki, M. Shikanai, H. Kobayashi and F. Okada, *Nutrients*, 2015, **7**, 10237–10250.

23 E. P. Ryan, A. L. Heuberger, T. L. Weir, B. Barnett, C. D. Broeckling and J. E. Prenni, *J. Agric. Food Chem.*, 2011, **59**, 1862–1870.

24 P. Daliu, A. Santini and E. Novellino, *Expert Opin. Ther. Pat.*, 2018, **28**, 875–882.

25 A. Santini, E. Novellino, V. Armini and A. Ritieni, *Food Chem.*, 2013, **140**, 843–849.

26 A. Santini and E. Novellino, *Expert Rev. Clin. Pharmacol.*, 2018, **11**, 545–547.

27 R. Andrew and A. A. Izzo, *Br. J. Pharmacol.*, 2017, **174**, 1177–1194.

28 S. Y. Shin, H. W. Kim, H. H. Jang, Y. J. Hwang, J. S. Choe, Y. Lim, J. B. Kim and Y. H. Lee, *J. Med. Food*, 2017, **20**, 855–863.

29 S. M. Boue, K. W. Daigle, M. H. Chen, H. Cao and M. L. Heiman, *J. Agric. Food Chem.*, 2016, **64**, 5345–5353.

30 T. Nguyen, M. Karl and A. Santini, *Foods*, 2017, **6**, E19, DOI: 10.3390/foods6030019.

31 H. Zhang, J. Wang, Y. Liu, L. Gong and B. Sun, *Food Funct.*, 2016, **7**, 2747–2753.

32 S. Gunasekaran, K. Venkatachalam and N. Namasivayam, *Mol. Cell. Biochem.*, 2019, **451**, 117–129.

33 E. Noaman, N. K. Badr El-Din, M. A. Bibars, A. A. Abou Mossallam and M. Ghoneum, *Cancer Lett.*, 2008, **268**, 348–359.

34 S. Phutthaphadoong, Y. Yamada, A. Hirata, H. Tomita, A. Hara, P. Limtrakul, T. Iwasaki, H. Kobayashi and H. Mori, *Oncol. Rep.*, 2010, **23**, 53–59.

35 S. Phutthaphadoong, Y. Yamada, A. Hirata, H. Tomita, A. Taguchi, A. Hara, P. N. Limtrakul, T. Iwasaki, H. Kobayashi and H. Mori, *Oncol. Rep.*, 2009, **21**, 321–327.

36 T. Shibata, H. Nagayasu, H. Kitajo, M. Arisue, T. Yamashita, D. Hatakeyama, T. Iwasaki and H. Kobayashi, *Oncol. Rep.*, 2006, **15**, 869–874.

37 T. Kuno, Y. Hirose, K. Hata, K. Kato, S. H. Qiang, N. Kitaori, A. Hara, T. Iwasaki, T. Yoshimura, K. Wada, H. Kobayashi and H. Mori, *Int. J. Oncol.*, 2004, **25**, 1809–1815.

38 M. Katayama, S. Sugie, N. Yoshimi, Y. Yamada, K. Sakata, Z. Qiao, T. Iwasaki, H. Kobayashi and H. Mori, *Oncol. Rep.*, 2003, **10**, 875–880.

39 D. Kim and G. D. Han, *Plant Foods Hum. Nutr.*, 2011, **66**, 285–290.

40 K. M. Kim, K. W. Yu, D. H. Kang and H. J. Suh, *Phytother. Res.*, 2002, **16**, 700–702.

41 L. M. Coussens and Z. Werb, *Nature*, 2002, **420**, 860.

42 A. Mantovani, P. Allavena, A. Sica and F. Balkwill, *Nature*, 2008, **454**, 436–444.

43 G. Trinchieri, *Oncology*, 2011, **25**, 418–420.

44 M. Gulhane, L. Murray, R. Lourie, H. Tong, Y. H. Sheng, R. Wang, A. Kang, V. Schreiber, K. Y. Wong, G. Magor, S. Denman, J. Begun, T. H. Florin, A. Perkins, P. O. Cuiv, M. A. McGuckin and S. Z. Hasnain, *Sci. Rep.*, 2016, **6**, 28990.

45 M. L. Justo, C. Claro, M. Zeyda, T. M. Stulnig, M. D. Herrera and R. Rodriguez-Rodriguez, *Eur. J. Nutr.*, 2016, **55**, 2011–2019.

46 K. Boonloh, V. Kukongviriyapan, B. Kongyingyo, U. Kukongviriyapan, S. Thawornchinsombut and P. Pannangpetch, *Nutrients*, 2015, **7**, 6313–6329.

47 Y. P. Rao, P. P. Kumar and B. R. Lokesh, *Lipids*, 2016, **51**, 451–467.

48 Y. P. C. Rao, D. Sugarsini and B. R. Lokesh, *Biochem. Biophys. Res. Commun.*, 2016, **479**, 747–752.

49 A. B. Kunnumakkara, B. Sung, J. Ravindran, P. Diagaradjane, A. Deorukhkar, S. Dey, C. Koca, V. R. Yadav, Z. Tong, J. G. Gelovani, S. Guha, S. Krishnan and B. B. Aggarwal, *Cancer Res.*, 2010, **70**, 8695–8705.

50 E. Pastille, A. Frede, H. J. McSorley, J. Grab, A. Adamczyk, S. Kollenda, W. Hansen, M. Epple, J. Buer, R. M. Maizels, R. Klopffleisch and A. M. Westendorf, *PLoS Pathog.*, 2017, **13**, e1006649.

51 T. Otto and P. Sicinski, *Nat. Rev. Cancer*, 2017, **17**, 93–115.

52 P. Hydbring, Y. Wang, A. Fassl, X. Li, V. Matia, T. Otto, Y. J. Choi, K. E. Sweeney, J. M. Suski, H. Yin, R. L. Bogorad, S. Goel, H. Yuzugullu, K. J. Kauffman, J. Yang, C. Jin, Y. Li, D. Floris, R. Swanson, K. Ng, E. Sicinska, L. Anders, J. J. Zhao, K. Polyak, D. G. Anderson, C. Li and P. Sicinski, *Cancer Cell*, 2017, **31**, 576–590.



53 H. Cai, E. A. Hudson, P. Mann, R. D. Verschoyle, P. Greaves, M. M. Manson, W. P. Steward and A. J. Gescher, *Br. J. Cancer*, 2004, **91**, 1364–1371.

54 W. Sun, W. Xu, H. Liu, J. Liu, Q. Wang, J. Zhou, F. Dong and B. Chen, *J. Nutr. Biochem.*, 2009, **20**, 276–284.

55 C. Park, N. Y. Jeong, G. Y. Kim, M. H. Han, I. M. Chung, W. J. Kim, Y. H. Yoo and Y. H. Choi, *Oncol. Rep.*, 2014, **31**, 1653–1660.

56 G. E. Hirsch, M. M. Parisi, L. A. Martins, C. M. Andrade, F. M. Barbe-Tuana and F. T. Guma, *Prostate*, 2015, **75**, 783–797.

57 S. Nurulhusna, M. E. Norhaizan, I. Hairuszah, M. A. Abdah, S. Norazalina and I. Norsharina, *J. Med. Plants Res.*, 2010, **4**, 2283–2289.

58 Y. M. El-Sherbiny, M. C. Cox, Z. A. Ismail, A. M. Shamsuddin and I. Vucenik, *Anticancer Res.*, 2001, **21**, 2393–2403.

59 A. Takashima, M. Ohtomo, T. Kikuchi, J. Iwashita, T. Abe and K. Hata, *J. Food Sci. Technol.*, 2013, **50**, 595–599.

60 N. H. Shafie, N. M. Esa, H. Ithnin, N. Saad and A. K. Pandurangan, *Int. J. Mol. Sci.*, 2013, **14**, 23545–23558.

61 A. A. Al-Fatlawi, M. Irshad, M. Zafaryab, M. M. Rizvi and A. Ahmad, *Asian Pac. J. Cancer Prev.*, 2014, **15**, 3731–3736.

62 C. K. Kong, W. S. Lam, L. C. Chiu, V. E. Ooi, S. S. Sun and Y. S. Wong, *Biochem. Pharmacol.*, 2009, **77**, 1487–1496.

63 A. Shibata, K. Nakagawa, T. Tsuduki and T. Miyazawa, *J. Nutr. Biochem.*, 2015, **26**, 832–840.

64 N. K. Badr El-Din, E. Noaman and M. Ghoneum, *Nutr. Cancer*, 2008, **60**, 235–244.

65 M. Ghoneum and S. Gollapudi, *Anticancer Res.*, 2005, **25**, 859–870.

66 M. Ghoneum and S. Gollapudi, *Cancer Lett.*, 2003, **201**, 41–49.

67 M. Ghoneum and S. Gollapudi, *Neoplasma*, 2011, **58**, 118–123.

68 Y. Horie, H. Nemoto, M. Itoh, H. Kosaka and K. Morita, *Appl. Biochem. Biotechnol.*, 2016, **178**, 1599–1611.

69 S. Kraus and N. Arber, *Eur. J. Cancer*, 2009, **45**(suppl. 1), 360–366.

70 J. Iqbal, M. Minhajuddin and Z. H. Beg, *Eur. J. Cancer Prev.*, 2004, **13**, 515–520.

71 G. M. Forster, K. Raina, A. Kumar, S. Kumar, R. Agarwal, M. H. Chen, J. E. Bauer, A. M. McClung and E. P. Ryan, *Food Chem.*, 2013, **141**, 1545–1552.

72 T. Kuno, S. Takahashi, H. Tomita, K. Hisamatsu, A. Hara, A. Hirata, H. Kobayashi and H. Mori, *Oncol. Lett.*, 2015, **10**, 3377–3384.

73 T. Kuno, Y. Hirose, Y. Yamada, K. Hata, S. H. Qiang, N. Asano, T. Oyama, H. Zhi, T. Iwasaki, H. Kobayashi and H. Mori, *Oncol. Rep.*, 2006, **15**, 533–538.

74 H. Tomita, T. Kuno, Y. Yamada, T. Oyama, N. Asano, Y. Miyazaki, S. Baba, A. Taguchi, A. Hara, T. Iwasaki, H. Kobayashi and H. Mori, *Oncol. Rep.*, 2008, **19**, 11–15.

75 T. Kuno, A. Nagano, Y. Mori, H. Kato, Y. Nagayasu, A. Naiki-Ito, S. Suzuki, H. Mori and S. Takahashi, *Nutrients*, 2016, **8**, E421.

76 M. Ghoneum, N. K. Badr El-Din, D. A. Ali and M. A. El-Dein, *Anticancer Res.*, 2014, **34**, 81–87.

77 S. Gollapudi and M. Ghoneum, *Cancer Detect. Prev.*, 2008, **32**, 1–6.

78 F. Edrisi, M. Salehi, A. Ahmadi, M. Fararoei, F. Rusta and S. Mahmoodianfar, *Eur. J. Nutr.*, 2018, **57**, 833–843.

79 A. Salar, S. Faghih and G. R. Pishdad, *J. Clin. Lipidol.*, 2016, **10**, 299–305.

80 S. Devarajan, B. Chatterjee, H. Urata, B. Zhang, A. Ali, R. Singh and S. Ganapathy, *Am. J. Med.*, 2016, **129**, 731–739.

81 A. Bumrungpert, R. Chongsuwat, C. Phosat and A. Butaenum, *J. Altern. Complement Med.*, 2019, **25**, 353–358.

82 Y. Ito, Y. Nakashima and S. Matsuoka, *Int. J. Med. Invest.*, 2015, **62**, 80–84.

83 A. F. Elsaid, M. Shaheen and M. Ghoneum, *Exp. Ther. Med.*, 2018, **15**, 2313–2320.

84 D. Cholujova, J. Jakubikova, B. Czako, M. Martisova, L. Hunakova, J. Duraj, M. Mistrik and J. Sedlak, *Cancer Immunol. Immunother.*, 2013, **62**, 437–445.

85 T. Kamiya, M. Shikano, M. Tanaka, K. Ozeki, M. Ebi, T. Katano, S. Hamano, H. Nishiwaki, H. Tsukamoto, T. Mizoshita, Y. Mori, E. Kubota, S. Tanida, H. Kataoka, N. Okuda and T. Joh, *J. Evidence-Based Complementary Altern. Med.*, 2014, **2014**, 828137.

86 A. M. Sheflin, E. C. Borresen, J. S. Kirkwood, C. M. Boot, A. K. Whitney, S. Lu, R. J. Brown, C. D. Broeckling, E. P. Ryan and T. L. Weir, *Mol. Nutr. Food Res.*, 2017, **61**.

87 D. G. Brown, E. C. Borresen, R. J. Brown and E. P. Ryan, *Br. J. Nutr.*, 2017, **117**, 1244–1256.

88 E. C. Borresen, D. G. Brown, G. Harbison, L. Taylor, A. Fairbanks, J. O'Malia, M. Bazan, S. Rao, S. M. Bailey, M. Wdowik, T. L. Weir, R. J. Brown and E. P. Ryan, *Nutr. Cancer*, 2016, **68**, 1269–1280.

89 Y. Itoh, M. Mizuno, M. Ikeda, R. Nakahara, S. Kubota, J. Ito, T. Okada, M. Kawamura, F. Kikkawa and S. Naganawa, *Evidence-based complementary and alternative medicine: eCAM*, 2015, **2015**, 974390.

90 M. H. Bang, T. Van Riep, N. T. Thinh, H. Song le, T. T. Dung, L. Van Truong, L. Van Don, T. D. Ky, D. Pan, M. Shaheen and M. Ghoneum, *Anticancer Res.*, 2010, **30**, 5145–5151.

