SYSTEMATIC REVIEW

Benefit of Asian pigmented rice bioactive compound and its implication in breast cancer: a systematic review [version 1; peer review: 2 approved, 1 approved with reservations, 1 not approved]

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Abstract

Background: Utilizing the bioactive compounds found in pigmented rice might significantly reduce the risk of breast cancer. This study aims to systematically review existing literature on the benefit of Asian pigmented rice bioactive compounds and their implication in breast cancer.

Methods: Searches of the literature were conducted in two databases (Scopus and PubMed) for a systematic review. The keywords resulted in a total of 407 articles, consisting of 103 PubMed and 304 Scopus articles. 32 manuscripts were excluded because the article was over 10 years old. After excluding book chapters and non-English languages, we had 278 potential articles to be reviewed. After checking and screening the title and abstract and eliminating duplicate articles, then 66 articles were obtained. After the selection and elimination of the full-text manuscripts, finally 10 of them which

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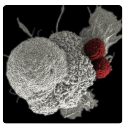
met the inclusion criteria.
Result: The included studies in this review were entirely based in Asia. The year of publication ranged from 2013 to 2020. Half of included studies used black rice extract, two used red jasmine rice extracts, and three used Korean rice extracts (black, red, dark purple and brown rice). All studies were conducted *in vitro* and three studies were compared with *in vivo* tests on female mice. The pigmented rice is mainly black, red, and dark purple rice, and contains a variety of peonidin-3-glucoside, cyanidin-3-glucoside, γ-oryzanol, γ-tocotrienol, proanthocyanidin, cinnamic acid, and anthocyanins that may act as pro-apoptotic, anti-proliferative, and anti-metastasis of the breast cancer cells.
Conclusion: Pigmented rice is a beneficial food which possessed bioactive compounds that may have significant potential concerning a breast cancer.

Keywords
medicine, cancer, non-communicable disease, rice, food



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Introduction

Most deaths throughout the world are now caused by non-communicable diseases (NCDs).[1] The recognition of the challenges of NCDs has become a global spotlight as stated in the sustainable development goals (SDGs) on the target 3.4 by 2030, reduce by one-third pre-mature mortality from NCDs through prevention and treatment, and promote mental health and wellbeing.[2] Cancer is one of NCDs that has become one of the leading causes of death worldwide with an estimate of 10.0 million deaths in 2020.[3]

An estimated 10.0 million people will die from cancer, a multifactorial illness, in the globe in 2020.[4] Breast cancer is the most diagnosed cancer type found in women and poses a serious public health concern globally.[5] An estimated breast cancer occurrence is 2.089 million in 2018 which is reported to increase continuously in all countries of the world.[3] There are major risk factors for breast cancer, such as aging, family history, reproductive factors, and life style.[6] Some of the factors are beyond individual controls and some are not. The factors that are within an individual's control that can be altered to minimize the chance of getting breast cancer, include diet and lifestyle.[7] Different food patterns may be one of the most fundamental factors for this.[8] Rice is a staple food of dietary calories for half of humanity and has been widely demonstrated as a chemopreventive component.[9] Whole-grain pigmented rice, in contrast to white rice, contains a higher concentration of bioactive phytochemicals with various health benefits.[8]

Due to the high levels of polyphenol and anthocyanins in colored rice, it is regarded as a functional food in Asia.[10] Many varieties of rice include colorful pigments, which are often concentrated in the pericarp or the bran of the rice kernel and give the grain hues like brown, red, purple, and black.[11] The flavonoids anthocyanin and proanthocyanidin, which are recognized to have nutritional benefits, are responsible for these color changes. However, their efficacy varies depending on rice color or variety.[12,13]

The presence of polyphenols, which have been shown to have antioxidant, anti-inflammatory, and anti-adipogenic potential in *in vitro* and *in vivo* investigations,[8,14] has been predominantly cited as the cause of the possible health advantages of this type of rice. Black, red, and brown rice bran's phenolic and flavonoid components, as well as their free and bound fractions, antioxidant and anti-proliferative properties, have all been documented.[13,15–17]

Thus, the aim of this study is to systematically review existing literature on the benefit of Asian bioactive compounds within pigmented rice and their implication in breast cancer.

Method

Search strategy

Articles for the current review were acquired from two electronic databases (PubMed and Scopus), considering that they hold the most articles for biomedical and pharmaceutical studies. The database literature search was conducted from November 8 to November 10, 2022. We created the keywords for each database. For PubMed, we used the following keywords; ((((((cancer) OR ("breast cancer")) OR (metastasis)) AND ((((((rice) OR ("pigmented rice")) OR ("black rice")) OR ("red rice")) OR ("purple rice")) OR ("brown ice")) AND ((("cancer therapy") OR ("anti-metastasis")). Meanwhile for Scopus, the keywords were "Cancer" OR metastasis OR "MCF-7" OR "Breast cancer" OR tumor AND "Pigmented Rice" OR rice OR paddy OR "Oryza sativa" AND "Cancer Therapy" OR medicine OR pharmaceutical OR physicochemical. During literature search, only free access articles were used.

Inclusion criteria

All types of experimental and observational studies written in English language were included. All duplicate studies and literature reviews were excluded from the final selection. Study subjects focused on breast cancer, and any other objects of *in vivo* and *in vitro* studies. Study factors included in the studies were the types of pigmented rice, other interventions in the form of extracts, whole grain, bran and hull. The research results include cancer therapy, pharmaceutical, and bioactive compounds as anti-cancer.

Study selection, data extraction, and quality assessment

The aforementioned keyword search resulted in a total of 407 articles, consisting 103 and 304 articles from PubMed and Scopus, respectively. We excluded 32 manuscripts because the article were published more than 10 years ago. After excluding book chapters and papers not in English, we had 278 potential articles to be reviewed. After checking and screening carefully the title and abstract of the manuscript, the duplicate articles were eliminated, then 66 articles were obtained. The authors reviewed the full text of those studies and finally selected 10 of them which met the inclusion criteria. 46 articles did not meet the criteria because duplicated, a book chapter, not accessible, not in English and no full-text. The flow diagram of the selection of study is shown in.[26,27]

Results

Characteristics of the articles

The included studies in this review were entirely of Asian. The year of publication ranged from 2013 to 2020. Five studies used black rice extract, two used red jasmine rice extracts, and three used a mixture of Korean rice extracts (black, red and brown rice). All studies were conducted *in vitro* and three studies were compared with *in vivo* tests on female mice. The summary of the included study were: tabulated based on the results, active compounds and sample breast cancer cell lines which are presented in Table 1.

Methodological quality

We reviewed results from 10 studies, seven of which involved *in vitro* experiment and three of which involved both *in vitro* and *in vivo* experiment. Unfortunately, there are no specific studies that focus on *in vivo* experiments. In detail, we report 10 samples from *in vitro* studies and three samples from *in vivo* studies.

In vitro

Many different cells have been used in *in vitro* experiments, including from human and murine breast cancer.[13,18–21] Besides, there are several single-cell *in vitro* studies, among which are subcutaneous MDA-MB-453 cells,[18,19] MCF-7 cells,[13] MDA-MB-231 cells,[20] and 4T1 cells.[21] Furthermore, several studies used multiple cells, such as,[15] which used HER2-positive (BT474, MDA-MB-453, and HCC1569 cells) and HER2-negative (MCF-7, SUM190, and MDA-MB-231) breast cancer cell lines. The HT1080 fibrosarcoma and MDA-MB-231 cell lines were utilized in.[22,23] The cells used by[16] were MCF-7, B16F10, M-3, and YD-38. The cells used by[24] were MCF-10A, MCF-7, and MDA-MB-453. In summary, the classification of breast cancer cells used in the 10 articles analyzed in this study were human triple-negative breast cancer (MDA-MB-231), human ERα-positive breast cancer (MCF-7), human HER2-positive breast cancer (BT474, MDA-MB-453, and HCC1569 cells), human HER2-negative (MCF-7, SUM190, and MDA-MB- 231), and murine breast cancer (4T1 and M3). There were also non breast cancer cell line used in this study, such as fibrosarcoma cell lines (HT1080), murine melanoma cell lines (B16F10), and human Squamous cell carcinoma cell lines (YD-38).

In vivo

Experiments *in vivo* using same species of mouse, naked female mice, were carried out with different cancer cells. Two studies employed 4-week-old mice,[18,21] while one used 6-7-week-old mice.[15] In these experiments, several cells types were used and injected into the flank of mammary fat pad of mice to construct the breast cancer mice model. HER2-positive MDA-MB-453 cells were employed in one study.[15] Besides, the previous study,[18] found MDA-MB-453 (ErbB2-positive) was employed alongside MCF-7 (ErbB2-negative) and MCF-10A (normal) cells. In the last study, 4T1 cells were used to be transplanted to the mice.[21]

The benefit of Asian pigmented rice bioactive compound

Pigmented rice cultivars differ in terms of both qualitative and quantitative characteristics.[10–12] This rice variety is distinguished by its mostly red, black, or purple pericarps. Wide-color rice varieties have drawn more attention because of their many biological functions. The pigments serve as sources of phytochemicals when contrasting the nutritional value of colored rice with white rice brans. Anthocyanidins, ferulic acid, diferulates, anthocyanins, and polymeric proanthocyanidins are some of the phenolic chemicals.[10,11]

Pigmented rice residues are attractive sources of bioactive substances such as phenolic antioxidants and anticancer agents for the benefit of human health.[12,13] Anthocyanin is found in the bran layers of the rice kernel, whereas phenolic acids are primarily present in the bran layers of rice in their free, conjugated, and bound forms.[16] The two primary bioactive phenolic chemicals found in cereal grains, mostly found in the pericarp of colored types, are anthocyanins and proanthocyanidins.[14] Anthocyanins, which are primary metabolites found in the bran layers of rice kernels, have been identified as functional dietary components that promote good health and have anticancer, antioxidant, hypoglycemic, and anti-inflammatory activities.[11]

Considering the numerous health benefits connected with functional components, such as anti-inflammatory, antioxidative, and anticancer properties, pigmented rice is considered an available food and food ingredient in many Asian countries.[10–14] The anticancer effect is suggested partly through the enhancement of bioactive substances such as vitamin E, phytic acid, γ-aminobutyric acid (GABA), γ-oryzanol, and phenolics.[9]

Table 1. The summary of studies discovered benefit of Asian pigmented rice physicochemical properties and its implication in breast cancer.[29]

Author, year	Derived from	Compound	Samples	Settings	Findings	Conclusions
Liu *et al.*, 2013	Black rice ethanolic extract using supercritical CO_2 extraction	Peonidine-3-glucoside and cyanidin-3-glucoside	Human breast cancer cell lines and mice breast cancer model	*In vitro* (BT474, MDA-MB-453, HCC1569, MCF-7, SUM190, and MDA-MB-231) *In vivo* (female nude mice)	A significant decrease of cell proliferation *in vitro* and tumor size *in vivo.* Anti-proliferative activity was mediated by the inhibition of phospho-HER2 phospho-AKT phopspho-p44/42MAPK, and apoptosis induction via caspase 3/7.	Peonidine-3-glucoside and cyanidin-3-glucoside compounds posed and potential as anti-proliferative and pro-apoptotic in breast cancer therapy.
Luo *et al.*, 2014	Black rice extract	BRA-90 anthocyanins (BRACs)	Human breast cancer cell lines	*In vitro* (MCF7, MDA-MB-453 and MCF10A) *In vivo* (female BALB/c mice)	In a concentration-dependent way, BRACs reduced the activity of urokinase-type plasminogen activator, a factor that promotes transfer, and they also inhibited migration, adhesion, motility, and invasion (u-PA). In addition, BRACs also diminished lung tumor nodules in mice and blocked pulmonary metastasis and tumor development.	Through the suppression of molecules that promote metastasis, BRAC has anti-metastatic potential against human breast cancer cells that are ErbB2-positive.
Chung *et al.*, 2015	Methanolic extract of three Korean cultivars rice; ilpum, Heugjinju, and Jeogjinju. And one japonica weedly rice cultivars; WD-3	3-Phenylpropanoic acid, 3,4-Dihydroxybenzoic acid, 2-Propenoic acid, 3-phenyl-, methyl ester, 2-Propenoic acid, 3-(4-hydrocxyphenyl)-, methyl ester, 2-Prepenoic acid, 3-(4-hydroxyphenyl)-, (Z)-, 2-Propenoic acid, 3-(3-hyroxyphenyl)-, methyl ester, Cinnamic acid [(2E)-3-Phenylacrylic acid, Hexadecanoicacid	Human breast cancer cell lines	*In vitro* (MCF-7)	The WD-3 hull extract decreased cell growth and induced G0/G1 phase arrest by inhibiting cyclins and cyclin-dependent kinases. Inhibition of p21 expression decreased the G1 phase arrest induced by WD-3 extract. Cinnamic acid derivatives were found to be the primary active ingredients in the F4 fractioned from WD-3.	The most phenolic substance was found in the pigmented wild rice hulls (WD-3). The primary ingredients that assist growth inhibition and cell cycle arrest in breast cancer cells are cinnamic acid and its derivatives.
Pintha *et al,* 2014	Ethanolic extract of red jasmine rice and its fraction (n-hexane, dichloromethane, and ethyl acetate	Proanthocyanidin, γ-oryzanol, γ-tocotrienol, γ-tocopherol	Human breast cancer lines	*In vitro* (HT1080 and MDA-MB-231)	Ethanolic ectract of red jasmine rice (ECC) and its fraction (hexane (Hex) and dichloromethane (DCM)) were able to inhibit HT1080 and MDA-MB-231 cancer cell invasion. However, the highest potency showed by Hex and DCM than ECC. Moreover, ethyl acetate fraction had no effect.	The anti-invasion potential of red jasmine rice extract caused by the activity of the bioactive content through the inhibition of MMPs secretion and activity.

Table 1. *Continued*

Author, year	Derived from	Compound	Samples	Settings	Findings	Conclusions
Pintha *et al.*, 2015	Ethanolic extract of red jasmine rice and its fraction (n-hexane, dichloromethane, and ethyl acetate	Proanthocyanidin	Human breast cancer cell lines	*In vitro* (MDA-MB-231)	Through the inhibition of ECM degradation-associated proteins like matrix metalloproteinase-9 (MMP-9), membrane type-1 matrix metalloproteinase, urokinase plasminogen activator, urokinase plasminogen activator receptor, and plasminogen activator-1, proanthocyanidin rich fraction from red rice (PRFR) inhibited MDA-MB-231 invasion. Additionally, it significantly reduced the release of intercellular adhesion molecule-1 and interleukin-6, as well as collagenase and MMP9 activities.	Proanthocyanidin from red rice (PRFR) inhibited the invasion of MDA-MB-231 breast cancer cells via modulating the expression of invasion-associated proteins, presumably by inhibiting NF-κB activity.
Baek *et al.*, 2015	Methanolic extract of three Korean cultivars; Ilpum, Heungjinju, Jeogjinju, and one Japonica weedy rice; WD-3	Phenolic Flavonoid	Human breast cancer cell lines	*In vitro* (MCF-7, B16F10, M-3, and YD-38 cell)	Pigmented rice bran and hull extracts had significantly higher levels of phenolic and flavonoidic compounds, DPPH radical scavenging activities, and reducing abilities than Ilpum extracts. In human breast, melanoma, and oral cancer cells, hull extracts shown more cytotoxicity than bran extracts, with Heugjinju hull extract being the most powerful. Cellular shrinkage, DNA breakage, and nuclear condensation suggest that hull extract-mediated.	Hull extracts showed greater potential than bran extracts in terms of cytotoxicity in human breast, melanoma, and oral cancer cells, where Heugjinju hull extract being the most potent.
Chen *et al.*, 2015	Black rice extract	Anthocyanins (BRACs)	Human breast cancer cell lines	*In vitro* (MDA-MB-453)	BRACs inhibited the migration and invasiveness of MDA-MB-453 HER+ cells through RAF/MAPK pathway showed by the inhibitory effect of BRACs against siRNA-mediated RAF/MEK/ERK pathway. In addition, BRACs also reduced the expression of metastatic related protein such as raf, mek, and jnk in MDA-MB-453 cells. This extract aslo tend to suppress the phosphorilation of RAF and MAPKs protein. The antimetastatic effect of BRACs was mediated by the ability of this extract on the inhibition of MMP2 and MMP9 expression.	BRACs suppressed the migration and invasion HER2+ breast cancer (MDA-MB-453) through the inhibition of RAF/MAPK pathway. Besides, BRACs also showed anti-metastatic effect mediated by the inhibition of MMP2 and MMP9 protein expression.

Table 1. *Continued*

Author, year	Derived from	Compound	Samples	Settings	Findings	Conclusions
Zhou *et al.*, 2017	Black rice extract	Anthocyanins (BRACs)	Human breast cancer cell lines	*In vitro* (MCF10A, MCF7, and MDA-MB-453)	BRACs inhibited the invasive ability of HER-2-positive human breast cancer cells, resulting in a 68% reduction in the number of invaded cells. They also reduced the HER-2-positive human breast's migration distance from cancer cells by 37% when compared to the control cells group that was not treated.	Metastasis suppression by BRACs mediated through cSrc/FAK/p130Cas pathway which is one the most pivotal pathway in breast cancer.
Ghasemzadeh *et al.*, 2018	Methanolic extract of black, red, and brown rice bran	Cinnamic acid, *p*-coumaric acid, catechin, myrecetin, and quercetin.	Human breast cancer cell lines	*In vitro* (MCF-7, MDA-MB-231, and MDA-MB-453)	Different coloured rice brans varied significantly in their phytochemical contents and biological activity. Black rice bran has the greatest phytochemical concentration, followed by red and brown rice bran. Except for ferulic acid and p-coumaric acid, the concentration of the free phenolic and flavonoid compounds was much greater than that of the bound compounds. Black rice bran extracts showed the highest antioxidant activity, followed by red and brown rice bran extracts. With half maximal inhibitory concentrations (IC50) of 148.6 and 119.2 mg/mL against MCF-7 and MDA-MB-231 cell lines, respectively, extracts of black rice bran demonstrated strong antiproliferative activity in contrast to the activity of the extracts of red rice bran (175.0 and 151.0 mg/mL, respectively) and brown rice bran (382.3 and 346.1 mg/mL, respectively).	The highest antioxidant and anti-proliferative activity was black rice extract followed by red and brown rice.
Teng *et al.*, 2020	Black rice extract	Anthocyanins (BRACs)	Murine breast cancer cell lines	*In vitro* (4T1) *In vivo* (female BALB/c)	BRE contained 25% anthocyanins inhibited the metastasis of 4T1 cancer cell lines by suppression EMT through the reduction of snail, vimentin, and E-cadherin expression. The *in vivo* study showed that this extract has no obvious systemic toxicity on the mice.	BRE able to suppress EMT and metastasis through the inhibition of metastasis related molecules. This extract has low toxicity and cause no obvious systemic toxicity.

Black rice

A traditional and healthy cuisine, black rice is mostly grown in East Asia. Phytochemicals, tocopherols, polyphenols, B vitamins, and anthocyanins are only a few examples of the water-soluble bioactive substances abundant in black rice.[21] These substances might help your health and shield you against long-term conditions linked to oxidative stress and antioxidant activity.[10] A significant amount of phytochemicals are present in black rice bran, giving it strong medicinal properties. Black rice extract anthocyanins dramatically decreased the metastasis of breast cancer, according to seven research that were considered. The aleurone layer of black rice is where black rice anthocyanins (BRACs) are found. Human breast cancer cells that are ErbB2-positive can be prevented from metastasizing by BRAC.[18] Additionally, Liu *et al.* (2013) demonstrated that black rice extract includes peonidin-3-glucoside and cyanidin-3-glucoside, which can diminish the tumor size and volume.[15]

Red rice

Two studies found that red jasmine rice, which contains proanthocyanidins, inhibits breast cancer cell proliferation. Most of the phenolic chemicals in red rice, which are responsible for the red coloring of the pericarp, are proanthocyanidins and catechins.[20,22] Proanthocyanidin from red rice (PRFR) contains procyanidins and prodelphinidins.[22] Moreover, red rice extract also has a high concentration of γ-oryzanol and γ-tocotrienol in the Hex and DCM fractions.[20]

Purple rice

A variety of rice varieties, including glutinous rice, are referred to as purple rice and have historically been eaten throughout Eastern and Southeast Asia.[23] The pigments are naturally occurring compounds belonging to the flavonoid family in which cyanidin, pelargonidin, peonidin, delphinidin, petunidin, and malvidin represent the most commonly occurring anthocyanin aglycone.[11] One study found that purple rice hulls contained the highest phenolic compound.[23] Cinnamic acid and its derivatives are the primary ingredients for breast cancer cell growth suppression and cell cycle arrest.[13]

Implication of bioactive compound in breast cancer

Phenolic and flavonoid chemicals act as an antioxidant to protect cells from oxidative damage, which is a common cause of aggressive diseases like cancer.[16] However, the anticancer activities were not directly correlated with total phenolic or total flavonoid content values.[16] So, phenolic and flavonoid from many types of pigmented rice have also been tested for apoptotic activity revealing that cell shrinkage and nuclear condensation occur in human breast cancer cell line MCF-7.[16] The antioxidant activity of rice phenolic compounds is detectable in parallel with the inhibition of proliferation of MCF-7 cells through G1 cell cycle arrest and comparable to quercetin as an antioxidant standart.[13]

Proanthocyanidins are monomeric flavan-3-ol oligo- or polymers that are created as a byproduct of the flavonoid biosynthesis process.[20] Proanthocyanidins, which are essentially concentrated tannins, are made by cytosolic multienzyme complexes acting along the phenylpropanoid route.[22] By incorporating sugars, anthocyanidins are transformed into anthocyanins.[19] Proanthocyanidins turn into anthocyanins when heated in an acidic medium. As byproducts of the flavonoid pathway, proanthocyanidins and anthocyanins have the same metabolic intermediates. Proanthocyanidins, in the form of procyanidin (catechin and/or epicatechin) and prodelphinidin (epigallocatechin and/or gallocatechin) showed anti-metastatic effects in cancer breast MDA-MB-231 and HT1080 cells.[22] It reduces the cell invasion and migration in a dose dependent manner with IC_{50} at 7.52±1.42 μg/mL and 10.6±0.59 μg/mL respectively and as a molecular mechanism of metastasis it inhibits collagenase activity.[20] Suppression of breast cancer metastasis including inhibition the mRNA expression of their signaling pathway has also been known.[19]

The anthocyanins pigment such as cyanin-3-glucosides or peonidin-3-glucosides known to dose-dependent inhibition of cell proliferation and suppress the tumour growth in HER2-positive cancer lines which associated with breast cancer.[15] Inherent with the previously studied that both compounds inhibit cell human ductal breast carcinoma HS578T growth by blocking cell proliferation at the G(2)/M phase so that it cannot form a normal mitotic apparatus, lowering some cancer response proteins, and chromatin condensation leads to cell death.[23] Anti-metastasis action prevents cancer cells from invading the blood or lymphatic vessel and spreading to other tissues or organs, among other benefits. The anthocyanins found in black rice are able to lower almost 40% of tumour nodules with *in vivo* studies and about 10% inhibits invasion of cancer breast MDA-MB-453 cells.[18] Aprevious study reported a higher invasive inhibition of cells by 68% and also a decrease in the migration distance of MDA-MB-453 cells by 37% with anthocyanins compared to untreated cells after 24 hours.[24]

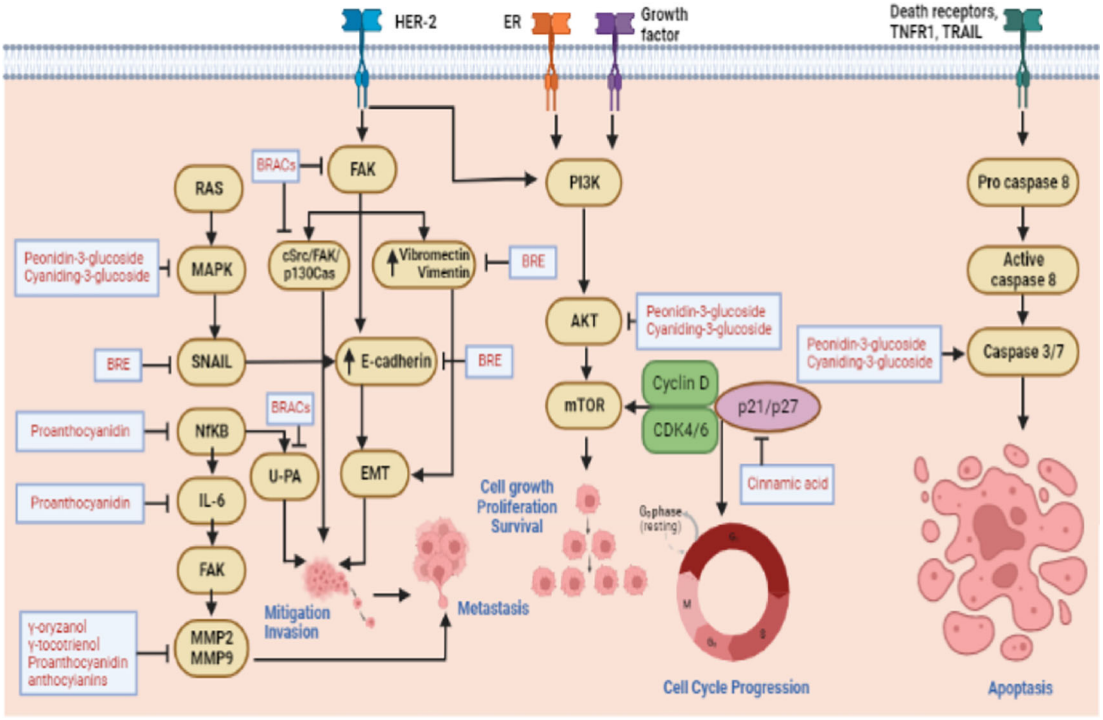

Figure 1. Pigmented rice bioactive compound possible mechanism from breast cancer.[28]

Strengths and limitations of the review

Several bioactive substances with the potential to operate as anti-metastatic agents, including anthocyanins, phenolics, and flavonoids found in different kinds of pigmented rice, are among the articles employed. To ensure the efficacy of each bioactive chemical, however, more *in vivo* research or randomized clinical trials with multicenter investigations are required as the majority of them are *in vitro* studies.

Significance of the findings and possible mechanism

Breast cancer is a complex and multifactorial disease that involves many cellular and molecular pathways. Weinberg and Hanahan in 2000 stated 6 hallmarks of cancer, (1) continuous proliferative signaling, (2) escaping growth suppression, (3) countering cell death, (4) sustaining replicative immortality, (5) promoting angiogenesis, and (6) metastasis.[25] To overcome this complex phenomenon, an effective therapy needs to be found. Due to the multi-target cancer therapy, natural product consumption is currently a major problem. As a result, this study investigated the bioactive chemicals found in Asian pigmented rice that were intended to target many pathways in the treatment of cancer (Figure 1).

This study found that bioactive compounds from the 10 articles reviewed, involved in several pathways on breast cancer, such as metastasis, cell growth and proliferative signaling, cell cycle progression and apoptosis.[13,15–24]

Black rice extract with unidentified compounds has anti-metastatis activity through the reduction of anti-metastasis related protein expression such as snail, vimentin, and E-cadherin.[21] Besides, peonidin-3-glucoside, cyaniding-3-glucoside from black rice, and cinnamic acid from WD-3 varieties of Korean rice showed anti-proliferative activity on breast cancer.[15] Peonidin-3-glucoside and cyaniding-3-glucoside of black rice also promoted apoptotic activity through the induction of caspase 3/7.[15,16] Anti-metastatic pathway was mostly found to be involved in the implication of pigmented rice bioactive compounds against breast cancer.[22] This study found that γ-oryzanol, γ-tocotrienol, and proanthocyanidin from red rice reduced MMP2 and -9 secretion.[22] In addition, MMP9 along with ICAM, IL-6, and NFkB were reduced after treated by red jasmine rice that contained proanthocyanidin.[20] Anti-metastasis also mediated by black rice anthocyanins through the reduction of FAK, cSrc and p130Cas phosphorylation. Black rice anthocyanins also posed anti-metastatic activity through the suppression RAF/MEK/ERK pathway and MMP2,-9 downregulation.[19] Lastly, black rice anthocyanins can suppressed u-PA involved in tumor invasion.[18]

Conclusions

The pigmented rice covered by this study were black, red, and dark purple rice, and all contains a variety of peonidin-3-glucoside, cyanidin-3-glucoside, γ-oryzanol, γ-tocotrienol, proanthocyanidin, cinnamic acid, and anthocyanins that may

act as pro-apoptotic, anti-proliferative, and anti-metastasis in breast cancer cells. Therefore, choosing whole-grain red, black, or purple is an excellent choice for health. Plus, these varieties are richer in disease-fighting antioxidants. Rice being a staple food for half of the world can be a source of energy for our generations only if it is accumulated with nutrition.

Data availability

No data associated with article.

Reporting guidelines

Figshare: PRISMA_2020_checklist. Pigmented Rice Bioactive Compound Possible Mechanism from Breast Cancer https://doi.org/10.6084/m9.figshare.21855495.[26]

This project contains the following reporting guidelines:

- PRISMA_2020_checklist.pdf

Figshare: Figure 1. PRISMA Flowchart. Pigmented Rice Bioactive Compound Possible Mechanism from Breast Cancer https://doi.org/10.6084/m9.figshare.21855582.[27]

This project contains the following reporting guidelines:

- Fig 1. tiff (PRISMA flowchart)

Acknowledgement

The author would like to thank Anjangsana Program Menuju Doktor Sarjana Unggul (PMDSU) 2022 from Human Resource Directorate, Ministry of Education, Republic of Indonesia for the support.

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Open Peer Review

Current Peer Review Status: ✗ ✓ ✓ ?

Version 1

Reviewer Report 16 October 2023

https://doi.org/10.5256/f1000research.143078.r213315

?

Yuan Seng Wu
Department of Biological Sciences, School of Medical and Life Sciences, Sunway University, Bandar Sunway, Selangor, Malaysia

The authors presented a systematic review on the Asian pigmented rice bioactive compounds and its implication in breast cancer. This manuscript is novel and has some values to the relevant community. Overall, the manuscript is acceptable in terms of writing and organisation. However, minor concerns as listed below should be addressed:

1. Title - the current title should be revised briefly to truly capture the content.

2. The authors should compare the included articles for the aspects in percentage. Like, how many articles (in percentage) presented or contained this compound or etc. Other than that, there were some missing words identified throughout the manuscript. Kindly check thoroughly.

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Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Yes

Is the statistical analysis and its interpretation appropriate?

Yes

Are the conclusions drawn adequately supported by the results presented in the review?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Molecular pharmacology and therapeutics

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 16 October 2023

https://doi.org/10.5256/f1000research.143078.r213312

Mohammed Aljunaid
Faculty of Medicine, Department of Dental Medicine, Taiz University, Taiz, Taiz Governorate, Yemen

I have completed my evaluation and after reading this Systematic Review carefully I am of the opinion that this manuscript should be considered for indexing.

Nonetheless, the authors need to resolve some minor difficulties such as the following:

In general check the grammar.

Methods:

1. The risk of bias needs to be added to the study or provide information on the quality assessment process.
2. Add the critical appraisal process to the review.

In the result:

1. It is important to strike a balance between providing enough detail to support the conclusions and maintaining readability.

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Yes

Is the statistical analysis and its interpretation appropriate?

Yes

Are the conclusions drawn adequately supported by the results presented in the review?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Periodontontology, Oral Medicine, and Oral Hearbal medicine

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 17 April 2023

https://doi.org/10.5256/f1000research.143078.r169259

Ananto Ali Alhasyimi
Department of Orthodontics, Faculty of Dentistry, Universitas Gadjah Mada, Yogyakarta, Special Region of Yogyakarta, Indonesia

Thank you for your work. The paper is well-researched and written, with profound insights into the bioactive compounds of Asian pigmented rice and their role in breast cancer. Best wishes to all the authors. I believe it has merit and should be considered for indexing. Novelty alone is sufficient and has a significant impact.
In order to improve its quality I think some minor issues should be noticed:

1. Please add the evaluation of the risk of bias in the included studies.

2. This systematic review was well-designed in accordance with PRISMA guidelines. It was included in the Reporting guidelines. Please incorporate the PRISMA flowchart into the primary text.

3. Since this is a review article, it is expected that you describe some of your own premises and elucidate some novel findings from your literature studies.

Are the rationale for, and objectives of, the Systematic Review clearly stated?
Yes

Are sufficient details of the methods and analysis provided to allow replication by others?
Yes

Is the statistical analysis and its interpretation appropriate?

Yes

Are the conclusions drawn adequately supported by the results presented in the review?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Orthodontic; biomaterials; biomechanic; retention in orthodontic

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 13 April 2023

https://doi.org/10.5256/f1000research.143078.r169255

Kok-Yong Chin
Department of Pharmacology, Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia

In this systematic review, the authors attempted to summarise the beneficial effects of Asian pigmented rice extract on breast cancer. However, the literature-gathering and evidence synthesis processes are flawed so the results and conclusion could not be judged fairly at this point. There is also no critical appraisal process, so it is hard to call this a systematic review.

- The systematic review was not constructed based on PRISMA guidelines. The authors should follow the guidelines and rewrite the manuscript for it to be considered. The authors could also refer to any published systematic review during their writing.
- Search string: Why was the bracket removed from the search string for the search in Scopus?
- Keywords: the inclusion of “cancer therapy” and “anti-metastasis” may restrict the search results. I recommend searching again without these terms.
- Setting open-access article as the inclusion criteria severely limits the search results.
- The authors need to justify setting a time frame of 10 years in the search. How would older articles not be relevant anymore?
- Why would the authors screen out items without original data (reviews, commentaries, letters etc) at the very last stage? This could be done earlier.
- Other necessary steps for deciding article inclusion are not illustrated: how many persons

are making the decision, how was discrepancy resolved etc.

- There is no PRISMA flow chart to summarise the entire literature search and article identification process.
- The data extracted in the evidence table were not complete. There were no dose and treatment period data.
- The Results and Discussion sections should be revamped. The results on the benefits of pigmented rice contain information that should appear in the introduction.
- The limitation of review section discussed more on the limitations of the research field, not on the review itself.

Are the rationale for, and objectives of, the Systematic Review clearly stated?
No

Are sufficient details of the methods and analysis provided to allow replication by others?
No

Is the statistical analysis and its interpretation appropriate?
Not applicable

Are the conclusions drawn adequately supported by the results presented in the review?
No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: osteoporosis, osteoarthritis, evidence synthesis, vitamin E, men's health

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 17 Apr 2023

Alexander Patera Nugraha

Dear honorable reviewer. First of all we would like to thank your valuable comments on our article. We will try to answer your review point per point as follows:

1. This article has considered and involved critical appraisal process, such as
   - Evaluation of the validity of the review

The methodological quality was assessed through the following points:

1. The question was clearly focused on breast cancer, study approach (*in vitro* and *in vivo*), intervention and outcome measures.
2. Inclusion criteria have been indicated clearly in the article.
3. Literature search method also has been clearly specified.

- Result interpretation

The result interpretation was done according to the study approach, the type of rice and bioactive compounds role in breast cancer. This interpretation covered overall questions of this review.

- Applicability of the results of the review

This review included possible mechanism and significance of finding that will be more applicable in health or pharmaceutical practice.

1. This article was constructed based on PRISMA guidelines and checklist.
2. This article also referred to one literature review.

Seechamnanturakit V, Karrila TT, Sontimuang C, *et al.*: The Natural Pigments in Pigmented Rice Bran and Their Relation to Human Health: A Literature Review. *KMUTNB Int. J. Appl. Sci. Technol.* 2018; **11**(1): 3–13.

Hopefully you could understand and approve this manuscript.
Thank you very much.
Sincerely Yours

Competing Interests: nil