

A Systematic Review of Phenolic and Flavonoid Compounds of *Oryza sativa* (Balatinaw Rice) Extracts against Cancer

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Submission Date: 27-08-2022; Revision Date: 11-10-2022.; Accepted Date: 30-10-2022.

ABSTRACT

This systematic review aims to determine the potential of bioactive compounds present in Balatinaw rice (*Oryza sativa*) extracts against the formation of cancer and aims to prove the promising bioactivity of *Oryza sativa* extract as medicinal plant. Cancer is an uncontrolled proliferation of aberrant cells in different parts of the body. The cancerous cells continuously replicate and replace the normal tissues. These changes of normal tissue into abnormal tissue can result in death and this is one of the most concerning causes of death in today's time. The Balatinaw rice (*Oryza sativa*) is a valuable natural resource that contains active chemical compounds, and it is one of the largest and most important staple food crops. This can aid in the development of a therapeutic drug and reduce the risk of certain disease such as cancer, diabetes, and cardiovascular disease. All chosen journals that were considered were thoroughly investigated and passed the systematic review criteria; 11 eligible journals from 2014 to present were utilized. The results show that *Oryza sativa* carries a bioactive compound which are the phenolic and flavonoid compounds. These two have a major role in minimizing the risks of inflammatory disorders. From the eleven (11) articles that were reviewed, six (6) of them present ferulic, *p*-coumaric acid, and gallic acid which were consistent to have in rice bran. All the three pigmented rice types have the reduction capacity in the viability of the following cancer cell lines. Also, studies have shown that the present phenolic and flavonoid compound in *Oryza sativa* extract has the capability to inhibit cancer cell proliferation and metastasizes while triggering apoptosis. Moreover, the phenolic and flavonoid compounds revealed a significant property, cytotoxic properties, which can stimulate cytolytic and antiproliferative to cancer cells. In conclusion, the biochemical activity of flavonoid and phenolic compounds present in *Oryza sativa* extract can be utilized as a therapeutic treatment against various cancers and considered as cheap and effective treatment.

Keywords: Cancer, Flavonoid, *Oryza sativa*, Phenolic.

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INTRODUCTION

In the recent years, cancer records the topmost causes of death worldwide. Cancer is an uncontrolled proliferation of aberrant cells in different parts of the body that damages DNA expressions. The cancerous

cells continuous to divide and replace the normal tissues, which can either be benign that stays in primary location without invading the other parts of the body, or malignant that can spread and invade the other tissues. The changes of normal cells are results from external agents includes chemical carcinogens, physical carcinogens, and biological carcinogens.^[1] Thus, a person's lifestyle contributes to the development of various cancers.

Balatinaw rice (*Oryza sativa*) is one of the most significant food crops to humans and one of the energy sources of an individual. In the recent study of Hoseinkhani

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DOI: 10.5530/ajbls.2022.11.85

et al.,^[2] crops like *Oryza sativa* have a high probability to develop a prevention in some diseases like cancer. Moreover, according to Ito and Lacerda,^[3] black rice has been shown to have numerous favorable impacts in individuals when consumed on a regular basis because grains like this carry bioactive compounds such as phenols and flavonoids.

The efficacy of plants as a form of treatment is mostly dependent on bioactive compounds. Phenols are a secondary metabolism in plants that has many good benefits on human's health. As a result, phenolic compound is considered as one of the most abundant phytochemical contents in grains; it contains a natural antioxidant, which acts as a free radical and can help to limit the oxidative stress-induced in biological molecules.^[4] In line with this, flavonoids have the ability to increase the potency of anti-cancer chemotherapeutic agents. Furthermore, this bioactive compound is eco-friendly and low cost.^[5] Phenolic and flavonoid compounds have mainly been known for their potential to improve human health by treating and preventing a variety of illnesses.

This systematic review aims to explore the potential of phenolic and flavonoid compounds present in *Oryza sativa* extract against cancer and to prove its significant biological activity as medicinal plant. The author's aim is to generate a new conclusion and to provide new information through a comprehensive systematic literature review. Moreover, these findings will contribute to the pharmaceutical industry in doing more investigations to utilize the *Oryza sativa* extract as therapeutic drug for different type of cancer, to develop a cheap but effective treatment and to aid in the prevention of cancer development worldwide.

MATERIALS AND METHODS

Literature Search

The background information of using *Oryza sativa* extracts to reduce cervical cancer formations presented in forms of relevant articles and literatures published from 2014-2022 were narrowed and gathered through conducting preliminary searches from various search engines such as Google Scholar, PubMed, and Science Direct. Most accurate results were produced through specifying key terms such as: "Phenolic Compounds", "Flavonoid Compounds", "*Oryza sativa*", and "Cancer". The title and abstract of the resulting studies were thoroughly evaluated to assure the level of relevance to the main study. The authors utilized the Mendeley Reference Manager to process all the references in this systematic review.

Eligibility Criteria

The inclusion criteria for this study were any published journal articles from Google scholar, PubMed, and Science Direct, between 2014 up to present, that reported the potential of Phenolic and Flavonoid compounds of *Oryza sativa* extract against cancer. Included studies were analyzed by the authors to generate a new conclusion. However, the exclusion criteria were: (1) cancer-free (2) reviews and mini-reviews (3) case reports (4) non-English text (5) no full text.

Data Selection and Strategy

All available data were extracted to probe the potential of phenolic and flavonoid compounds of *Oryza sativa* extracts against cancer. To ensure the relevance and reliability of all information gathered from the selected studies, screening of the article was divided into two phases: the first phase of the screening began with eight (KT, MV, RT, EB, VDP, AD, CG, AP) authors filtering journals based on the exclusion and inclusion criteria and the second phase of the screening was completed by three authors (EB, VDP, CG) who finalized the relevant journals to the studies and approved the articles. Research titles, abstracts, methods, and results were reviewed

conscientiously in this phase of the screening. The set of data of this systematic review includes the name of the author(s), date of publication, rice variations, technique used in plant extraction, and the total percentage of phenolic and flavonoid compounds. All data were extracted into Microsoft Excel spreadsheets for future reference.

A total of 152 articles were collected using the key terms in the given search engines:

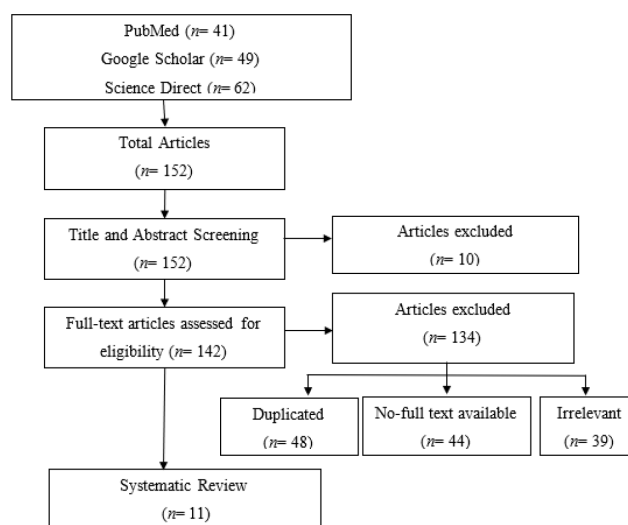


Figure 1: Flowchart of the literature search process.

PubMed, Google Scholar, and Science Direct. All 152 articles went through title and abstract screening in which 10 articles were excluded. A total of 142 articles were screened for their full-text eligibility in which 134 articles were excluded due to the following: 39 articles were considered irrelevant, 48 articles were duplicates, and 44 articles were having no full-text availability. A total of 11 articles were screened and will be used for the systematic review.

RESULTS

Cancer Type	Rice Variation	Cell Line	In vitro/ vivo	Phytochemical Compound			Significant Findings	Ref
				Phenolic	Content	Flavonoid		
Prostate Cancer	(Purple rice) <i>Oryza sativa</i> L.	PC3	<i>In vitro</i> and <i>in vivo</i>	RBC3G	10-50 µM		Anti-cancer agent RBC3G inhibits prostate cancer transformation, including cell proliferation, transformation, migration, and invasion. The natural cyanidin-3-glucoside could suppress PC3 cancer cell behaviors or EMT features by reversing the EMT process with the right concentration. Thus, it appears to contribute to cancer prevention rather than anti-cancer therapy.	[14]
No Specific Cancer	(Black Rice) <i>Oryza sativa</i> L.	HepG2 FL83B	<i>In vitro</i>	Protocatechuic acid Orientin 3,3,4,5,5,7	18.51 mg/g 22.89 mg/g		The phytochemical content of black rice leaf extracts was found to be high, corresponding to an increase in antioxidant capacity.	[11]
No specific cancer	(Red rice) <i>Oryza sativa</i> L.	MDA-MB-231 HT1080		Hexahydroxy flavanone γ-tocotrienol	8.51 mg/g Hex: 2.78 µg/ml DCM: 1.97 µg/ml Hex: 127.55 µg/ml DCM: 94.85 µg/ml		The high concentration of γ-oryzanol and γ-tocotrienol in the Hex and DCM fractions of red rice extract showed anti-invasion capability via inhibition of MMP secretion and activity. While the proanthocyanins is the one responsible in the anti-invasion measures of the CEE fractions.	[10]
Breast Cancer	(Black, Brown, Red) <i>Oryza sativa</i> L.	MCF-7 MDA-MB-231		Cinnamic acid p-coumaric acid	25.53 mg/100 g 33/35 mg/100 g	Quercetin Catechin Myricetin	All the three pigmented rice types have the reduction capacity in the viability of the following cancer cell lines such as MCF-7 and MDA-MB-231. However, the MDA-MB-231 cells were known to be significantly sensitive to the treatment.	[4]
Liver Cancer	White Rice bran Purple Rice bran			Protocatechuic acid Tocotrienols p-coumaric acid Vanillic acid 4-Hydroxybenzoid acid	7.12 mg 202.6 mg 0.35 mg 4.73 mg ND	Peonidin-3-glucoside Cyanidin-3-glucoside	The protocatechuic acid and other phenolic compounds present in PRBE were found to be anti-carcinogenic. Tocotrienols have been demonstrated to inhibit cancer cell proliferation, induce cancer cell apoptosis, and modulate the expression of proinflammatory cytokines.	[8]

Cancer Type	Rice Variation	Cell Line	In vitro/ vivo	Phytochemical Compound			Significant Findings	Ref
				Phenolic	Content	Flavonoid		
Breast cancer	Black Rice	MCF-7 (HER 2-negative) MDA-MB-453 (HER-2 positive) MCF-10A	In vitro		Anthocyanin	ND	BRACs inhibited the adhesion, migration, and invasion of HER-2 positive breast cancer cells in humans. It also boosted E-cadherin expression in epithelial cells while decreasing fibronectin and vimentin expression in mesenchymal cells. As a result, the anti-metastatic actions of BRACs are mostly due to their inhibitory influence on EMT.	[6]
Breast cancer Colon Cancer Prostate Cancer Lung Cancer Esophageal cancer					Anthocyanin	ND	Anthocyanin found in black rice helps to prevent fatty liver disease in breast cancer cells. It also aids in the prevention of carcinogenesis by inhibiting cancer progression and spreading through cell signal transduction. Lastly, it also assists in the prevention of breast cancer growth by inducing apoptosis and scavenging of reactive oxygen species.	[16]
Cervical Cancer	Black Rice) <i>Oryza sativa</i> L.	HeLa Cells	In vitro		Anthocyanin	ND	Anthocyanin found in the methanolic extracts of black rice (<i>Oryza sativa</i> L.) has decreased the cell proliferation and viability of HeLa cells.	[12]
No specific Cancer	<i>Oryza sativa</i> L. cultivars: <i>Mushki budgi</i> <i>Mushki kandi</i> <i>Kamad</i> <i>Koshkari</i>		In vitro				Aromatic rice cultivars with higher free phenolic content have higher potential bioavailability and thus antioxidative activity. By functioning as anti-carcinogens, these phenolics play an important role in ensuring therapeutic effects.	[15]
No specific Cancer	(Black and White rice) <i>Oryza sativa</i> L. cultivars: IR 64 Cempo Ireng Woja Laka Toraja	HepG2 Raji cells Vero cells					With an IC ₅₀ value of more than 1000 µg/ml, the extracts of Cempo Ireng and Toraja cultivars showed no cytotoxic effect against all cell lines. In contrast, the Woja Laka cultivar showed cytotoxic effects on HepG2 and Raji cells. Among the four cultivars, only IR 64, which is a white rice cultivar, showed cytotoxic effect on all cell lines.	[13]

DISCUSSION

Flavonoids and phenolics are natural occurring substances that can be seen in plants which are said to help minimize the risk of a variety of chronic inflammatory disorders, including diseases like cancer, diabetes, and cardiovascular disease. In line with this, we reviewed the phenolic and flavonoid compounds present in *Oryza sativa* that aids in cancer activity through a comprehensive literature review. In the research study of Zhou *et al.* (2017),^[6] it shows that the anthocyanins can be used as an anticancer drug. Since anthocyanins is one of the common flavonoids which exists in some fruits and vegetables, it has a significant effect when it comes to cancer. However, in the study of Khoo *et al.* (2017),^[7] the anthocyanins came from plants have a capacity to be included in the ingredients in formulating an anticancer drug. Dokkaew *et al.* (2019)^[8] stated that anthocyanins also play a role in the reduction of cancer cell formation. This is through derived colored vegetables and fruits that improve the body's intracellular antioxidant systems and be able to detoxify enzyme activities, which can result to the said reduction of cell formation. Anthocyanins also showed various chemopreventive effects that can suppress multiple cancers such as liver, colon and breast cancers. In addition to the study "Phytochemical constituents, antioxidant activity, and antiproliferative properties of black, red, and brown rice bran",^[4] it was stated there that they used an ultra-high performance liquid chromatography (UPLC) to help differentiate the phenolic compounds as well as the flavonoid compounds. It was also mentioned that the quercetin, catechin, and myricetins are one of the flavonoid compounds. Wherein these three can be seen in the variations of *Oryza sativa*. Quercetin, catechin, as well as myricetin can be found in plants wherein their flavonoid compound can help out to reduce the risk of infection. Thus, this can also be used as an anti-carcinogenic, anti-inflammatory.^[9] In addition to that, quercetin also has the ability to modulate metabolic activation of carcinogen by inhibiting CYP1A1, an extrahepatic enzyme and AhR gene.^[8]

Phenolic compounds are a class of molecules that play a role in plant growth and development as well as defensive mechanisms. One of the phenolic compounds in *Oryza sativa* is proanthocyanidin. It was demonstrated that proanthocyanidins that are derived from various kinds of medicinal plants, is known to possess anti-metastasis effect on cancer cells. It is also stated that the anti-invasion activity of crude ethanolic extract fraction of *Oryza sativa* can be partly due to the effect of the phenolic compound proanthocyanidin.^[10]

In the study "Evaluation of Phytochemical Contents and *in vitro* Antioxidant, Anti-Inflammatory, and Anticancer Activities of Black Rice Leaf (*Oryza sativa* L.) Extract and Its Fractions", protocatechuic acid, a natural phenolic acid found in many nutritional diets, is one of the principal phenolic compounds found in *Oryza sativa*. This research suggests that this compound can help decrease tumor cell proliferation.^[11] Another article entitled "Phytochemical constituents, antioxidant activity, and antiproliferative properties of black, red, and brown rice bran"^[4] states that black rice bran is the one with rich source of antioxidants, where a total of five phenolic compounds were detected, namely protocatechuic acid, syringic acid, ferulic acid, cinnamic acid, and p-coumaric acid. In line with the previous studies presented, protocatechuic acid and other phenolic acid metabolites are also present in purple rice bran extract which possess anti-carcinogenicity.^[8] Phytochemical screening was done in several studies to determine the phenolic content and compound present in *Oryza sativa*. Alkaloids, phenols, glycosides, flavonoids, tannins, terpenoids, and carbohydrates are confirmed to be abundant in black rice based on the methanolic extraction conducted. Despite the fact that these phytochemicals are secondary metabolites with no nutritional value, they have been shown to have disease-preventive qualities and may play a vital part in all biological functions.^[12]

Studies have shown that Black rice (*Oryza sativa*) appears to have phenolic and flavonoid compounds which are capable of stimulating cytolytic and proliferative cells while simultaneously being toxic and antiproliferative to cancer cells. In accordance with this, Rukmana *et al.* (2016)^[13] stated that phenolic and flavonoid content of Black and White rice (*Oryza sativa* L.) are recognized to be a source of phytochemical substances that can help prevent certain cancers. And to further support this, Dokkaew *et al.* (2019)^[8] revealed that flavonoid and phenolic compounds exhibited a cancer chemopreventive action. According to their study, flavonoids like quercetin and kaempferol have been demonstrated to alter carcinogen metabolic activity. Anthocyanins, a kind of natural flavonoid, shows to have characteristics of antioxidant, anti-inflammatory, anti-cancer and anti-metastasis.^[6] Moreover, greatest amount of flavonoid and phenolic compounds in black rice bran as well as in red and brown rice were also identified in the study of Ghasemzadeh *et al.*^[4] showing that ferulic acid and p-coumaric acid were the most prevalent phenolic compound, whereas flavonoid compound such as catechin and myricetins were most abundant in brown and red rice bran, and

apigenin and quercetin in black rice bran. From the eleven (11) articles that were reviewed, six (6) of them present ferulic, *p*-coumaric acid, and gallic acid were consistent to have in rice bran. All the three pigmented rice types have the reduction capacity in the viability of the following cancer cell lines such as MCF-7 and MDA-MB-231. Tons of research revealed that other pigments of the extracted husk of the rice provide a wide range of physiological bioactive constituents. Red rice extract, in particular, has demonstrated potent antioxidative, anti-inflammatory, and anti-cancer cell proliferation properties. The bioactivities of red rice extract were reported to contribute to their pharmacological activities, which has been primarily comprised of phenolics, flavonoids. It also showed that the anti-metastasis ability of the extracts of the red rice on human cancer cells and this can recognize the bioactive components in some of those fractions.^[10] Moreover, the study of Rukmana *et al.* (2017)^[13] revealed that those who have a phytoconstituents of the black rice is influenced by means of the anthocyanin. Compounds such as the phenols, flavonoids, *γ-oryzanol* can be used in the anti-cancer and anti-inflammatory.

CONCLUSION AND RECOMMENDATION

Phenolic and flavonoid compounds have been proven to be abundant in *Oryza sativa* making it an excellent material in preventing cancer progression. The use of these chemicals has risen dramatically in recent years. The authors structurally analyzed the various phenolic and flavonoid compounds and their metabolic routes in this systematic review, as well as their derivatives in cancer treatment and prevention. It was found that most of the antioxidant activity in plants and plant products were attributed to the largest category of phytochemicals which is phenolics and the flavonoid which is the most prevalent group of naturally occurring phenolic compounds - plays an important function in the anti-inflammatory and anti-cancerous effects. The anti-cancer properties of flavonoids were attributed to their ability to influence signal transduction pathways within cancer cells. Also, flavonoid chemicals can decrease cell proliferation and metastasize while inducing apoptosis. Flavonoids like anthocyanin, quercetin, catechin and myricetin prevent cancerous cell formation. They are also described as disease-preventive supplements and is an ideal candidate for chemo preventive drugs due to their low toxicity. Phenolics, on the other hand, have significant cytotoxic characteristics, the capacity to metastasize as well as the potential to proliferate in cancer cells, thus making them useful in cancer

chemoprevention. Additionally, they boost the immune system's capability to identify and destroy cancer cells while also preventing the creation of new blood vessels which are required for cancer progression. They also reduce cancer cells' adhesiveness and invasiveness, lowering their cellular proliferation. As a result, the biochemical activity of flavonoid and phenolic compounds present in *Oryza sativa* can be utilized as a therapeutic treatment against various cancers

This study suggests that *Oryza sativa* should be regarded as a safe and effective cancer preventive and treatment method. It is highly recommended that the findings of this systematic review could be used to encourage the consumption of *Oryza sativa* and its usage in food production which will help to enhance human health. In addition, the role of these phytochemicals, as well as their mechanism of action should be further explored. The human application whether it is *in-vivo* or *in-vitro* could be investigated further in the development of cancer treatments and drugs.

ACKNOWLEDGEMENT

The completion of this paper would not have been possible without the support and guidance of the authors' research adviser, Mr. Daniel Bercede, RMT, MSMT. The authors would like to express their deepest gratitude and appreciation for his willingness and expertise in this subject and research writing. Errors have been corrected thoroughly throughout the writing process making this paper as precise and accurate as they have envisioned.

The authors are greatly indebted to their research professors, Ms. Michelle San Luis, RMT, Mr. Earl Adrienne Abella Cano, RMT, Ms. Charlene Princess S. Tolenada, RMT, and Mr. Bernardino M. Hagosojos, RMT. Their input and attention to detail heavily influenced the progression of the research paper. With consistent constructive feedbacks, the authors were able to deliver concepts concisely.

Above all things, the authors are grateful for the exceptional support and guidance from their family, friends and colleagues at Far Eastern University. They wish to thank them for providing endless encouragements and serving as a beacon that had led and will continue to lead them to success and accomplishments.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

SUMMARY

Cancer is the major cause of death worldwide, it is due to uncontrolled proliferation of cells which metastasize, invade nearby tissues, and ultimately to other parts of the body. Phytochemicals found in *Oryza sativa* have been known to exhibit anti-inflammatory, anti-proliferative, anti-cancer, and anti-oxidative property. These phytochemicals that make up the Balatinaw rice (*Oryza sativa*) are found as well in foods like berries, vegetables, coffee, and etc. Phenolics are compounds that account for the highest anti-oxidant activity in plants. Whereas, flavonoids are naturally occurring phenolic compounds that can also be found in different plant parts. Studies have shown that the bioactive component of Balatinaw rice extract including: phenolic and flavonoids have the ability to inhibit cancer cell proliferation, and metastasis. All journals are conscientiously reviewed using selection criteria to assure their validity. These chosen journals were collected in a reputable sources. The findings of the chosen publication include anti-cancer activity of flavonoids in influencing signal transduction pathways within cancer cells, low toxicity of flavonoid compounds as a candidate in chemo-preventive therapy and reducing ability of phenolic compounds on the cancer cell's adhesiveness and invasion capability. This revealed that the phenolic and flavonoid extract found in rice bran have anti-cancer and anti-inflammatory ability which can be used as an alternative drug that is cheap and cost-effective against various cancer.

AUTHOR'S CONTRIBUTION

The following authors have substantially contributed to the accomplishment of the first and second draft of the manuscript including the author who led and conceptualized the study, Kent Talosig (KT), and co-members, Marie Vargas (MV), Ralph Tolentino (RT), Erika Bischocho (EB), Vince De Pano (VDP), Angelica Diolanda (AD), Chiara Garcia (CG), and Arlene Parale (AP). Preliminary searching of articles was done by all these authors and was screened by author CG, EB, VDP, and RT. Discussion of the results was accomplished by author VDP, AD, MV, RT, KT and AP. Conclusions were made by author KT and AP based on the findings of the study. Author KT and MV wrote the abstract of the study while author CG made the acknowledgment part of the study. Overall, reading of the final manuscript was done by all authors.

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Cite this article: Talosig KA, Vargas MB, Tolentino RC, Bischocho EG, De Pano VB, Diolanda AB, Garcia CL, Parale AC, Bercede DH. A Systematic Review of Phenolic and Flavonoid Compounds of *Oryza sativa* (Balatinaw Rice) Extracts against Cancer. *Asian J Biol Life Sci*. 2022;11(3):640-6.