REVIEW

Anti-Oxidant, Pro-Oxidant and Anti-Inflammatory Effects of Unpolished Rice Relevant to Colorectal Cancer

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Abstract

Colorectal cancer (CRC) is a major worldwide health problem owing to its high prevalence and mortality rates. Carcinogenesis in the colon is a multistage and multifactorial process. An imbalance between free radical exposure and anti-oxidant defense systems may leads to oxidative stress and attack of macromolecules which can alter signal transduction pathways and gene expression. Consequently, oxidative damage can lead to cellular dysfunction and contribute to pathophysiological processes in a variety of diseases including CRC. One factor tightly associated with CRC is chronic inflammation, which can be present from the earliest stage of tumor onset. Unpolished rice is an attractive chemoprevention in CRC due to their anti-oxidant and anti-inflammatory activities. The aim of this paper is to review evidence linking oxidative stress and inflammation to CRC and to provide essential background information for understanding future research on oxidative stress and inflammation on CRC. Mechanisms of action of unpolished rice in CRC carcinogenesis are also discussed.

Keywords: Colorectal cancer- oxidative stress- anti-oxidants- inflammation- unpolished rice

Asian Pac J Cancer Prev, **17 (12)**, 5047-5056

Colorectal cancer (CRC) is commonly regarded as a Western lifestyle disease that is a major cause of morbidity and mortality throughout the world (Center et al., 2009; Haggar and Boushey, 2009; Tanaka, 2009). It is estimated that 69,090 men and 63,610 women will be diagnosed with CRC in 2015 (Siegel et al., 2015). CRC is the third most common cancer in men and the second in women worldwide. In Asian countries, it has become an important problem and its incidence is rising rapidly due to the changes in dietary and lifestyle factors to more westernization (Moghimi-Dehkordi and Safaee, 2012). In Thailand, CRC is the first ranking of cancer incidence in men (16.2%) and the third in women (9.6%). Additionally, the number of CRC cases will be predicted to increase each year caused by the change of Thai dietary habits (Chindaprasirt et al., 2012). The increasing prevalence of westernization styles will likely continue to the growing international CRC burden if these behaviors are not modified (Center et al., 2009).

The etiology of CRC is complex and attributable to the actions of inherited and environmental factors (Pandurangan and Esa, 2013). Approximately 5% of CRC cases occur in an inherited form, which is associated with well-defined syndromes such as hereditary nonpolyposis colorectal cancer and familial adenomatous polyposis (FAP). However, the largest fraction of CRC cases occurs in a sporadic form (95%), which has been linked to environmental factors rather than heritable genetic changes (Fleming et al., 2012). Chronic intestinal inflammation and dietary are the environmental factors that have been reported to be the major causes of CRC development (Candela et al., 2014).

Chronic inflammation has linked with two- to three-fold greater lifetime risk of developing CRC (Saxena et al., 2013). Several epidemiological studies have indicated that CRC is strongly associated with diet, and thus it may be possible to prevent its occurrence by dietary modifications (Slattery et al., 1999; Pandurangan et al., 2012; Pandurangan and Esa, 2013). CRC is considered to be linked with dietary habits like excess fat intake. The progressive intake of western diet which high in fat and low in fiber has been reported to increase the incidence of CRC. In contrast, the high consumption of fruits and vegetables could be decreased the risk of CRC (Pandurangan, 2013).

Dietary chemoprevention has an attractive new strategies approached for CRC treatment. There are convincing evidences that lifestyle and dietary risk factors strongly associated with increased or decreased risk of CRC. Chemoprevention which involved the use of phytochemicals and even whole plan extracts to prevent, combat or reverse the processes of cellular and molecular in carcinogenesis due to its multiple intervention strategies (Neergheen et al., 2010). Unpolished rice, a highly sources of phytochemicals has been shown the strongest association with CRC chemoprevention. The aim of this review is to provide a literature on the effects and some mechanisms of dietary unpolished rice on CRC

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chemoprevention.

Colorectal carcinogenesis

Carcinogenesis is a multistep process that develops through a series of genetic changes with the transforming step of normal cells into a malignant phenotype (Bretthauer, 2010). The whole process can be divided into three main stages: initiation, promotion and progression. There are multiple events in each step. Initiation, a rapid and irreversible process, is defined as exposure of normal cells to carcinogenic agents including chemical, ionizing and pathogenic agents. These agents can induce the change at the genomic level. Promotion, a relatively lengthy and reversible process, involves proliferating preneoplastic cells accumulation. Progression, the final stage of neoplastic transformation, involves the growth of a tumor, tumor invasion and metastasis (Kinzler and Vogelstein, 1996).

In human lesions, the genes, such as K-ras, adenomatous polyposis (APC), deleted in colorectal cancer (DCC) and p53, are frequently mutated or deleted. K-ras and APC gene mutations are involved in relative early stages of colon carcinogenesis. The APC gene has been identified as responsible for the inherited CRC syndrome such as familial adenomatous polyposis. The Wnt/APC/β-catenin signaling plays an important role in chemical-induced colorectal carcinogenesis in both rat and human (Takahashi and Wakabayashi, 2004).

CRC is defined as any malignant neoplasm arising from the inner lining of the colonic epithelium (Rajamanickam and Agarwal, 2008). Gross pathology of CRC can occur in a pedunculated polyp, sessile polyp mass or stricture. In a term of histology, CRC is classified as well differentiated, moderately differentiated, or poorly differentiated tumor (Cappell, 2005).

Aberrant crypt foci (ACF), precancerous lesions of CRC were proposed as a histological lesion that preceded polyp formation in colorectal carcinogenesis (McLellan and Bird, 1988). Previously, ACF have been hypothesized as the earliest detectable abnormality of colorectal carcinogenesis (Bird and Good, 2000). These lesions can be seen in the mucosal surface of colon after staining with methylene blue and observed under the microscope (Bird, 1995). The characteristic of ACF shows as the thicker epithelial linings, larger in diameter, and showing darker staining than the surrounding normal crypts. They slightly elevate and protrude from the epithelial lining toward the lumen (Norlida and Phang, 2010).

The progression of ACF formation can be determined by the number of aberrant crypts (ACs) which present in each ACF called crypt multiplicity. ACF with increasing crypt multiplicity represent an advancing precancerous lesion (Bird, 1995). As time progresses, ACF develop as varying grades of dysplasia which correctly called microadenoma (Roncucci et al., 1991). Microadenoma can grow and associate with the macroscopic adenoma, they also develop to adenocarcinoma (Archer et al., 1992).

Oxidative stress

Radicals are the collective term consist of free radicals and non radicals, they can be called oxidants (Halliwell, 2007). Free radicals such as superoxide anions (O2•-), hydroxyl radicals (HO•), peroxide radicals (ROO•), and nitric oxide (NO•) are molecules, atoms or ions that contain unpaired electron in outer orbit. They are highly unstable and active toward chemical reactions with other molecules (Perse, 2013). Non radicals, such as hydrogen peroxide (H2O2), Peroxynitrite (ONOO−), singlet oxygen (1O2) do not have unpaired electrons (Poljsak and Dahmane, 2012), but they react similarly to free radicals and can easily lead to free radical reactions in living organisms (Halliwell, 2007; Perse, 2013). In addition, non-radical molecules can support redox reactions of reactive species in the body (Trachootham et al., 2008). Depending on which atom is in the active radical molecule, compost of reactive species that are derived from molecular oxygen (ROS) and nitrogen (RNS). Recently, chlorine (RCS), bromine (RBS) and sulphur-derived (RSS) radical species have also been identified (Rizzo et al., 2010).

Sources of free radicals

Free radicals and other reactive species are generated from either endogenous or exogenous sources. Internally, they are produced as a normal part of metabolism within the mitochondria, peroxisomes, infection, immune cell activation, inflammation, phagocytosis, ischemia and physical exercise (Lobo et al., 2010). In addition, physiological factors such as mental status like stress, emotion and disease conditions are also responsible for the formation of free radicals (Dayem et al., 2010). Exogenous or external factors that help to promote the production of free radicals are smoking, alcohol, environmental pollutants, cooking (smoked meat, used oil and fat), heavy or transition metals (Cd, Hg, Pb, Fe, As), radiation, certain drugs, pesticides, industrial solvents and ozone (Pham-Huy et al., 2008; Lobo et al., 2010).

Oxidative stress and cancer

Normally, the homeostasis of radicals and anti-oxidants in organisms is very important for normal metabolism, signal transduction and cellular function (Rizzo et al., 2010). An imbalance between the radicals and anti-oxidant defense systems leads to oxidative stress (Perse, 2013). The excessive radicals in oxidative stress can attack macromolecules including lipids, carbohydrates, proteins and DNA (Bhattacharyya et al., 2014). In addition, they can alter signal transduction pathways and gene expression (Trachootham et al., 2008). Consequently, the oxidative damage can lead to cellular dysfunction and contributes to promote the pathophysiological processes of a variety of diseases (Zhao et al., 2005).

In human, chronic oxidative stress is considered as a major cause of cancer (Khansari et al., 2009). Cancer patient has been associated with the high levels of oxidative stress markers such as ROS, nitric oxide (NO), oxidative DNA damage and lipid peroxides (Perse, 2013). Oxidative DNA damage has been proposed to be critically involved in carcinogenesis (Mates et al., 2008). 8-hydroxy-2'- deoxyguanosine (8-OHdG) and 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG) are considered the markers of oxidative DNA damage. The higher levels of the 8-OHdG and 8-oxodG have been proved to be the potentially important factors of initiation

and promotion in carcinogenesis (Valavanidis et al., 2009). Malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE) are main products of lipid peroxidation (Perse, 2013). MDA can react with DNA to form adducts with deoxyguanosine, deoxyadenosine and deoxycytidine (Bastide et al., 2011). Additionally, higher levels of proteins modified by the 4-HNE and peroxynitrite (ONOO-) have been detected in cancer (Kondo et al., 1999).

In cancer cell, the relatively large amounts of radicals, especially H2O2 have an important role in cell function. The constitutive high production of H2O2 in cancer cells appears to promote cell proliferation. H2O2 mediates signal transduction, leads to the transcriptional activation of cyclooxygenase-2 (COX-2) and matrix metalloproteinase (MMP). COX-2 protein is involved in the induction of growth factor phosphorylation and mitogenic signaling (Pai et al., 2002). MMP genes code proteins facilitate tumor invasion and metastasis (Westermarck and Kahari, 1999). However, high amount of H2O2 above a certain threshold causes cell cycle arrest and/or apoptosis (Loo, 2003). An exposing HT-29 colon cancer cells to H2O2 can activate ERK, JNK, and p38 MAPK which subsequently induce apoptosis (Chien et al., 2014). In addition, the cancer cells are more susceptible to be killed by anticancer drugs with oxidative stress-related apoptosis than the normal cells because cancer cells are already near a threshold for tolerating free radicals (Wang and Yi, 2008). Thus, ROS either stimulates or inhibits the proliferation of cancer cells depending on the concentrations of ROS (Loo, 2003).

Inflammation and colorectal cancer

Inflammation is a physiological process that responses to tissue damage resulting from microbial infection, pathogen infection, chemical irritation and/or wounding. Dysregulation of inflammation resolution causes cellular response alteration to the pattern of chronic inflammation (Philip et al., 2004). Chronic inflammation is a well- recognized risk factor of human CRC (Kinugasa and Akagi, 2016). It acts as host defense mechanism against infection or injury and is primarily a self limiting process, inadequate resolution of inflammatory responses that lead to various disorders including cancer. Inflammation can promote carcinogenesis in various steps such as induction of genomic instability, alteration in epigenetic events, enhanced proliferation, resistance to apoptosis, induction tumor angiogenesis, and induced invasion and metastasis (Balkwill and Mantovani, 2001; Rakoff-Nahoum, 2006; Kundu and Surh, 2008; Porta et al., 2009). Patient with long-standing inflammatory bowel diseases (IBD) including Crohn's disease (CD) and ulcerative colitis (UC), have an increased risk of developing CRC (Sengupta et al., 2016). Several molecular events involved in chronic inflammatory process may contribute to multi-step carcinogenesis of CRC (Raskov et al., 2014).

Chronic inflammation is involved in all stages of carcinogenesis. Reactive oxygen species (ROS), reactive nitrogen species (RNS) or other reactive species generated from inflamed tissue can cause genomic instability which leads to initiation of carcinogenesis. In the early stage, tumor cells disrupt the homeostasis of surrounding tissue by various mechanisms such as direct cell-cell contact, communication between cell and extracellular matrix (ECM) and secretion of various factors which can accelerate the inflammation.

Cytokines, key regulators of immune responses in cancer, secreted by many cell populations and tumor cells cause inflammatory cells infiltration in the tumor microenvironment. These inflammatory cells function to release several pro-inflammatory mediators, such as cytokines, chemokines, growth factors and prostaglandins in order to maintain inflammatory tumor microenvironment, stimulate cell proliferation and promote angiogenesis (Kundu and Surh, 2008). Cytokines can be classified based on their function into Th1-type and Th2-type cytokines. Th-1 type cytokines such as interleukin (IL)-12, IL-15 and interferon gamma (IFN-γ), contribute to cellular immune responses which are essential for an effective response against tumor cells. Th2-type cytokines such as IL-4, IL-5, IL-6, IL- 10 and IL-13 can suppress the tumor specific immune response. CRC development is accompanied by alteration of cytokine production, which is polarized from Th1-type into Th2-type cytokines in the colorectal adenoma-carcinoma sequence (Cui and Florholmen, 2008). Several pro-inflammatory cytokines have been shown to regulate growth of cancer through the contribution of both tumor promotion and tumor progression. Among these cytokines, IL-6 is regarded to take a center stage of cancer development in human. An increased IL-6 expression has been detected and associated with poor prognosis patients of both sporadic and colitis-associated CRC (Waldner et al., 2012). IFN-γ, pro-inflammatory cytokine, has been known to be one of the most important Th1-type cytokines. This cytokine has also been identified as an important modulator of immune-related genes such as nuclear factor-kappa B (NF-κB), it has both of immune- regulatory and anti-tumor properties which may play a critical role in carcinogenesis (Gambhir et al., 2015).

The multi-step process of CRC from normal colonic epithelium to invasive colon carcinoma is supported by the tumor microenvironment which can promote tumor growth, angiogenesis and metastasis. The tumor microenvironment consists of tumor-infiltrating cells, vasculature, ECM, and other matrix-associated molecules (Peddareddigari et al., 2010). Tumor-infiltrating cells predominantly contain tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), mast cells, cancer-associated fibroblasts (CAFs), monocytes, neutrophils, CD4 T-cells, CD8 T-cells, dendritic cells (DCs), natural killer cells (NK), endothelial cells, endothelial progenitor cells (EPCs), platelets and mesenchymal stem cells (MSCs). These cells are able to maintain tumor-associated inflammation, angiogenesis and immunesuppression which promote tumor growth and metastasis (Peddareddigari et al., 2010).

Chemoprevention of colorectal cancer

Chemoprevention is a pharmacological approach to arrest, reverse and retard the process of carcinogenesis (Sporn and Suh, 2000). Chemopreventive agents are

natural, synthetic or biologic compounds (Henderson et al., 2012) which are subdivided into two main categories: 1) Blocking agents prevent carcinogens from reaching the target sites, from undergoing metabolic activation, and from subsequently interacting with crucial cellular macromolecules. 2) Suppressing agents inhibit the malignant transformation of initiated cells, in either the promotion or progression stage (Surh, 2003).

Chemopreventive agents should have 1) little or no toxicity, 2) high efficacy in multiple sites, 3) capability of oral consumption, 4) known mechanisms of action, 5) low cost, and 6) human acceptance. Several natural products such as fruits, vegetables, medicinal plants and herbs play a crucial role in the protective effects against CRC. In particular, they consist of a wide variety of biologically active phytochemicals including phenolics, flavonoids, carotenoids and alkaloids which have been shown to suppress early and late stages of carcinogenesis (Rajamanickam and Agarwal, 2008). Their phytochemicals have been known to interfere with molecular pathways that involved in CRC carcinogenesis. They can block initiation or reverse the promotion stage of colorectal carcinogenesis (Surh, 2003).

Wnt/β-catenin signaling pathway plays a critical role in the regulation of cell proliferation and carcinogenesis of CRC in both rodents and human. The activation of this pathway is important for both initiation and progression of CRC. Therefore, it is becoming a promising target for chemoprevention in CRC (Pandurangan and Esa, 2013). Several chemopreventive phytochemicals, such as curcumin, caffeic acid, epigallocatechin gallate (EGCG), quercetin, resveratol, luteolin, phytic acid and genistein, have been revealed to downregulate the Wnt/β-catenin signaling pathway (Surh, 2003; Rajamanickam and Agarwal, 2008; Xiao et al., 2008; Pan et al., 2011; Pandurangan et al., 2012; Pandurangan, 2013). The relationship between inflammation and CRC has been demonstrated by increased risk of CRC development with IBD as well as the effectiveness of anti-inflammatory drugs to decrease colorectal tumors. Chronic inflammation of colon is closely associated with the CRC incidence.

Cyclooxygenase 2 (COX-2) is considered to be a molecular target for CRC prevention. Moreover, various chemopreventive agents can modulate the target gene expression which is the key of cancer processes involving cell proliferation, differentiation and inflammation (Brown and DuBois, 2005; Kim and Milner, 2007; Rajamanickam and Agarwal, 2008; Tanaka, 2012; Pandurangan and Esa, 2013). The potential targets such as β-catenin and COX-2 have been more studied and identified as useful targets of chemopreventive agents to prevent CRC by regulation of Wnt/β-catenin and COX-2 pathways (Pandurangan, 2013; Pandurangan and Esa, 2013). COX-2, the rate-limiting enzyme, is required for prostaglandin biosynthesis which is induced by a wide spectrum of growth factor and proinflammatory cytokines. It is also overexpressed in the transition from colorectal adenoma to CRC. The over-expression of COX-2 can promote tumorigenesis through the direct actions on the stromal compartment resulting in the tumor angiogenesis. COX-2 inhibitor has emerged as an approach to the prevention of CRC which can suppress colon polyps both in animal models and in patients with FAP. Therefore, the inhibition of COX-2 is a critical step due to it is directly involved in the progression of CRC (Koehne and Dubois, 2004; Pandurangan and Esa, 2013).

Phytophenolics

Phytophenolics are bioactive substances that widely distributed in plants (Shahidi and Wanasundara, 1992). Phenolic compounds are a class of compounds containing one or more hydroxyl group (-OH) bonded directly to an aromatic hydrocarbon group. Natural phenolic compounds are classified as phenolic acids, flavonoids, and polyphenols or tannins based on the number of phenol ring in the molecule. (1) Monocyclic phenols are phonolic compounds that consist of one phenol ring including phenols and phenolic acids. Phenolic acids have a carboxyl group linked to benzene ring. The difference among phenolic acids can be distinguished depending on their structures (Khadem and Marles, 2010). (2) Flavonoid groups are phenolic compounds carried 2 phenol rings that called dicyclic phenols. The flavonoids are the largest studied of natural phonolic compounds which include several thousand compounds such as flavonols, catechins, flavanones, anthocyanidins and isoflavonoids. (3) The large complex structure of phenolic compounds is polycyclic phenols or polyphenol. This class includes lignins, catechol melanins and flavolans (condensed tannins) (King and Young, 1999).

Phytophenolics and anti-oxidant activity

Phytophenolics play an important role in the anti-oxidant activity. They may directly scavenge some reactive species including hydroxyl, peroxyl and superoxide radicals (Rice-Evans et al., 1996). Some phenolic compounds may bind pro-oxidant metals such as iron and copper, this mechanism can prevent the formation of free radicals (Halliwell, 2007). Previously, phenolic compounds are strongly associated with the increased activity of anti-oxidant enzymes (Chiang et al., 2006). Thus, phenolic compounds are considered to be dietary anti-oxidants which against oxidative stress-related diseases including cancer.

Phytophenolics and chemopreventive activity

Not only antioxidant activity, phytophenolics also play a crucial role in health-promoting properties, especially in cancer chemopreventive activity. The anti- tumorigenesis effects of phytophenolics are to induce enzymes involved in detoxicating the chemical carcinogens (Pandey and Rizvi, 2009). Phenolic compounds can inhibit the carcinogenesis (Watson et al., 2000), they prevent a new tumor growth or limit the proliferation of cancer cells (Loo, 2003). Interestingly, phytophenolics also induce the formation of H2O2 to achieve an intolerable level of high oxidative stress in cancer cells (Long et al., 2000). Previously, epigallocatechin gallate (EGCG), quercetin and gallic acid generated H2O2 in time- and dose-dependent manners in culture media of cancer cells (Loo, 2003). Curcumin induced cancer cell apoptosis through the formation of ROS that promoted single-strand breaks in DNA of Jurkat T- lymphocytes (Kelly et al.,

2001), and induced ASK1-MKK4-JNK stress signaling pathway in human gastric cancer cells (Liang et al., 2014). Resveratrol, high phenolics in grapes activated GSH efflux that is capable of inducing apoptosis in human leukemic monocyte lymphoma cell line (Guha et al., 2011). These data could be suggested that phytophenolics modulated the oxidative stress in cancer cells, thereby the affecting signal transduction, activation of redox-sensitive transcription factors, and expression of specific genes that related to cancer cell apoptosis (Loo, 2003).

Unpolished rice

Rice belongs to the genus Oryza and the tribe Oryzeae of the family Gramineae (Poaceae). The genus Oryza contains 25 recognized species, of which 23 are wild species and two, O. sativa and O. glaberrima are cultivated (Ge et al., 1999). The cultivated rice (Oryza sativa L.) is the predominant species which is the second largest produced cereal in the world (Chen et al., 2004). Rice, a major staple food crop, has been consumed over a half of the world's population. It is an important crop in Asian countries and has been reported as a good source of phytonutrients. It is mostly consumed as white rice, removal of the bran from the grain, which is obtained by milling and polishing brown rice.

The whole grain rice contains insoluble phenolic compounds which are formed during grain maturation and possess potent anti-oxidant property (Shao et al., 2014). Phenolics exhibit a wide range of biological effects such as anti-inflammatory, anti-carcinogenic, anti-bacterial, anti-viral, hepatoprotective and vasodilatory actions. They are known to reduce the risk of several chronic diseases such as colon cancer, cardiovascular disease, obesity and diabetes. However, they are normally lost with the rice bran during the process of polished rice (Okarter and Liu, 2010).

Brown rice, an unpolished whole grain, is obtained by the removal of the outermost layer or the hull of the rice kernel which is the least damage to its nutritional values. It is commonly known to contain large amounts of dietary fiber, vitamins and minerals, and therefore is considered to be more nutritious and healthy in comparison with polished rice. The complete milling and polishing that converts brown rice into white rice can destroy over a half of vitamin B, minerals, dietary fiber and essential fatty acids (Itoh et al., 2012). Epidemiological studies suggest that the consumption of whole grains is inversely associated with the incidence of intestinal adenomatous polyps and the fiber from whole grains. It also significantly associated with a lowered risk of chronic diseases and CRC (Jacobs and Steffen, 2003; Schatzkin et al., 2008). Interestingly, unpolished rice has been shown the strongest association with CRC chemoprevention in human. The consumption of unpolished rice at least once a week reduced the risk of colorectal polyp formation by 40% (Tantamango et al., 2011).

Anti-oxidant and pro-oxidant activities of unpolished rice on CRC

Anti-oxidant activity

Unpolished Thai rice presents many color varieties (Chen et al., 2004). Many studies reported that rice containing colored pigments had higher anti-oxidant activity than that of non-colored rice (Shao et al., 2014). Previously, high levels of anti-oxidant activities and phenolic compounds were associated with the colored pigments in plants (Odabasoglu et al., 2004). The red color Thai rice had higher phenolic content than that of all black strains from Thailand, China, and Sri Lanka (Rattanachitthawat et al., 2010; Sompong et al., 2011). High phenolic content was strongly correlated with the colored pigments of rice, the radical scavenging activity of colored Thai rice was directly proportional to the phenolic content (Rattanachitthawat et al., 2010). Moreover, unpolished Thai rice contained high levels of anthocyanin pigment, phenolic content and antioxidant activity (Suwannalert and Rattanachitthawat, 2011), the consumption of unpolished Thai rice has been associated with low level of malondialdehyde (MDA), an oxidative stress marker in rats (Suwannalert et al., 2010). In addition, unpolished Thai rice has been shown to inhibit ACF formation in AOM-induced rats through oxidative stress defense mechanisms (Tammasakchai et al., 2012). Recent study also showed the effect of Brewers'rice that decreased the number of ACF with dysplastic morphology in a dose-dependent manner in AOM-treated rats (Tan et al., 2016) and this rice also improved the antioxidant levels in these model (Tan et al., 2015).

Pro-oxidant activity

Many studies reported that the colored rice and their phytophenolics had cytotoxic effects on various cancer cell types through the induction of apoptosis. Cyanidin and malvidin in dark purple rice had growth inhibitory effects on human monocytic leukemia (U937) cells by promote the arrest of G(2)/M phase of cell cycle and induce apoptosis (Hyun and Chung, 2004). Rice bran-derived phytophenolics inhibited cells proliferarion and induced cell apoptosis in several cancer cells types, such as breast, lung, liver and colon (Henderson et al., 2012). Black rice pericarp extract inhibited cell proliferation and induced apoptosis in human prostatic cancer (PC-3) cells (Jiang et al., 2013). Methanolic purple rice extract exhibited the inhibitory growth effect on human hepatocellular carcinoma (HepG2) cells by induced cell apoptosis via the mitochondrial pathway with the loss of mitochondrial transmembrane potential (MTP) and the activation of caspase-3 and -9 (Banjerdpongchai et al., 2014). Rice bran extract of purple riceberry at low dose had ability to prevent H2O2- induced oxidative stress in CaCo-2 cells, but it exerted a promoting effect on intracellular H2O2-induced oxidative stress in the high dose (Summart and Chewonarin, 2014). Thus, phytophenolics not only exert anti-oxidant activity but also can exert pro-oxidant activity based on certain concentrations (Dai and Mumper, 2010). These properties may be caused by the presence of transition alkali or metal ions which mediated autoxidation of phytophenolics to generated more radicals, especially H2O2 (Joubert et al., 2005; Labieniec and Gabryelak, 2006). These suggestions were possible that a pro-oxidant activity of phytophenolics can be acted as chemopreventive agent that plays a crucial role in CRC

prevention and/or therapy.

The unpolished Thai rice was shown to increase CaCo-2 cells death in a dose dependent manner by induce cellular apoptosis and might be associated with the increased of cellular oxidative stress (Tammasakchai et al., 2015). This study was the same as previous study, brown rice fermented with Aspergillus oryzae extract exerted oxidative damage and induced apoptosis in human colorectal cancer (HCT116) cells (Itoh et al., 2012). Overall experiments indicated that phytophenolics-rich unpolished rice may be bioactive work as CRC chemopreventive agent through the modulation of cellular oxidative stress-induced apoptosis.

An intracellular redox balance, especially GSH/GSSH status has been related to oxidative stress control which plays a key control in intestinal growth regulation (Noda et al., 2001). ROS can alter the GSH/GSSG ratio which is associated with the inducing apoptosis in cancer cells (Holmgren et al., 2005). The previous study was shown the levels of GSH and GSSG in CaCo-2 cells that unpolished Thai rice extract at the cytotoxic doses at 5 and 7.5 mg/ml showed significantly induced the depletion of GSH level in a dose dependent manner (Tammasakchai et al., 2015). This result is related to previous studies, some phytophenolics can activate GSH depletion and induce apoptosis (Guha et al., 2011; Traverso et al., 2013). The low level of GSH associated with the inhibition of cancer cell growth and proliferation (Obrador et al., 1997), whereas the high GSH is important in apoptosis evasion of cancer cells (Franco et al., 2009).

Anti-inflammatory activity of unpolished rice on colorectal cancer

One of the promising strategies of attractive chemopreventive agents is to alleviate inflammatory responses. Chronic inflammation is involved in all stages of CRC carcinogenesis and has linked with two- to three-fold greater lifetime risk of developing CRC (Kundu and Surh, 2008; Terzic et al., 2010; Saxena et al., 2013). The relationship between inflammation and cancer has been made on the basis of various observations, for instance, tumors arise at the sites of chronic inflammation, inflammatory cells are present in tumors, and overexpression of cytokines can induce cancer. Epidemiological studies have revealed that chronic inflammation can increase the risk of numerous cancers (Kraus and Arber, 2009).

COX-2 expression plays a role to enhance cancer development in the situation of chronic inflammation (Lu et al., 2006). High expression of COX-2 also associated with inflammation process. Overexpression of COX-2 in most cancer cells is found to stimulate cellular proliferation, enhance angiogenesis, enhance tumor invasiveness and inhibit apoptosis. The functional relationship between COX-2 in linking inflammation to cancer has been become excessive study. Polyphenols are known to be powerful anti-oxidants and free radical scavengers which also have anti-inflammation properties. Polyphenolic compounds such as red wine and black tea have been reported to modulate COX-2 expression in AOM-induced rats (Luceri et al., 2002). Unpolished rice was shown to decrease COX-2 expression in dose dependent manner in AOM-induced rats (Reungpatthanaphong et al., 2016). Furthermore, the study revealed the correlation between COX-2 overexpression and cytoplasmic β-catenin expression which has been reported in recent studies, suggesting a local interaction between β-catenin and COX-2 molecules to progress the growth and invasion of CRC (Kazem et al., 2014). Previous studies reported that COX-2 expression may be enhanced by Wnt/ β-catenin signaling pathway (Kawasaki et al., 2007; Nunez et al., 2011; Shafie et al., 2013). It is supposed that unpolished Thai rice may down regulate Wnt signaling pathway via the inhibition of β-catenin, then decreasing COX-2 expression.

Cytokines, key regulators of immune responses, modulate tumor growth and tumor microenvironment through mediating interactions between cancer cells and infiltrating inflammatory cells (Kantola et al., 2012). In AOM-treated rats, the serum values of IL-6 and IFN-γ were elevated in all groups with AOM induction implicating inflammation involvement (Reungpatthanaphong et al., 2016), which are similar to the prior studies. Previously, several studies have been reported to increase IL-6 expression in the serum of patients with CRC and also associated with tumor stage, size, metastasis and survival of CRC patients (Chung and Chang, 2003; De Vita et al., 2004; Knupfer and Preiss, 2010). Clinical and experimental data have been proposed that IL-6 contributed to both sporadic and colitis-associated CRC development (Waldner et al., 2012). In addition, increased serum level of IL-6 has been shown in animal models of colitis-associated CRC induced by AOM (Greten et al., 2004). Serum level of IFN-γ has also been shown to increase in chronic disease (Iyer et al., 2007). Recently, serum IL-6 and IFN-γ profiles were found to be significantly higher in CRC patients than in those of healthy controls (Kantola et al., 2012). These findings suggested that increased levels of proinflammatory cytokines are strongly associated with the risk of CRC. Unpolished Thai rice effectively decreased serum levels of proinflammatory cytokine expression, IL-6 and IFN-γ, in dose dependent manner. It is strongly indicated that unpolished Thai rice decreased inflammatory reactions in AOM-induced rats by downregulation of proinflammatory cytokine responses (Reungpatthanaphong et al., 2016).

IL-10 is an anti-inflammatory cytokine produced primarily by macrophages, regulatory T cells and epithelial cells (Moore et al., 2001). It was regarded as an immune suppressive cytokine that hindered anti-tumor immunity (Dennis et al., 2013). IL-10 exerted both of anti-inflammatory and anti-tumor effects which inhibited tumor growth. IL-10 deficient mice have been shown to develop colitis and then colitis-associated cancer within two to three weeks after birth (Sturlan et al., 2001). In previous studies, high level of IL-10 expression was shown to correlate with poor survival of cancer patients (Sarris et al., 1999; Visco et al., 2004), whereas some other studies showed contrary results (Soria et al., 2003; Toiyama et al., 2010). Therefore, deep insight into the controversial functions of IL-10 in chronic diseases and cancer is important required (Zhao et al., 2015). The pretreated with unpolished rice in AOM-induced rats has increased level

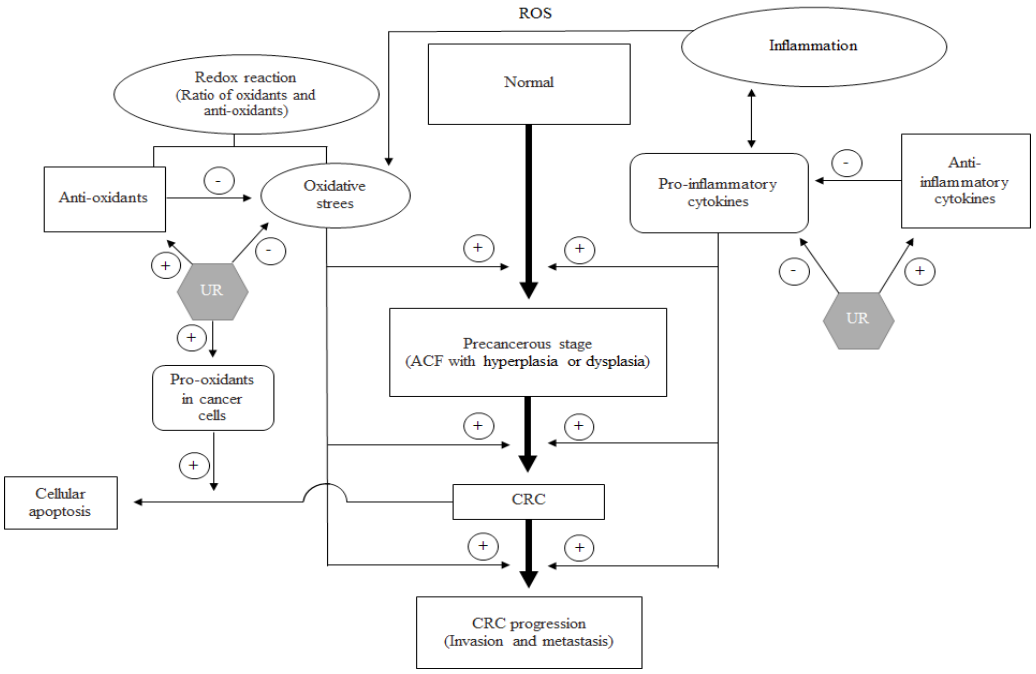

Figure 1. Proposed Schematic Diagram of Oxidative Stress and Inflammation Induced CRC Development and Progression. ACF , Aberrant crypt foci; CRC , Colorectal cancer; ROS, Reactive oxygen species; UR , Unpolished rice; + , Induction/promotion; - , Inhibition/suppression

of IL-10 (Reungpatthanaphong et al., 2016). It is indicated that IL-10 controls inflammatory reaction by suppressing the expression of pro-inflammatory cytokines which is similar to previous studies. IL-10 has been reported to inhibit the production of pro-inflammatory mediators by monocytes and macrophages such as IFN-γ, IL-6, IL-8 and tumor necrosis factor -α (TNF-α). Inhibition of IL-10 is overcome by increasing IFN-γ concentration which was the competitive interaction between two cytokines pathways (de Waal Malefyt et al., 1991; Moore et al., 2001). However, the effect of IL-10 is quite complex which is still considered as anti-inflammatory and immunosuppressive properties.

Numerous studies confirming the close relationship between chronic inflammation and oxidative stress in CRC carcinogenesis has encouraged many researchers to be concerned with chemopreventive treatment by using natural product, one of the powerful sources of anti-oxidative and anti-inflammatory activity is the unpolished rice. Beside of their anti-oxidative activity, they act as either anti-oxidant or pro-oxidant effect to CRC. Likewise, the anti-inflammatory activity of unpolished rice that effect by simultaneously decreased levels of certain proinflammatory cytokines and the associated signaling pathway and elevated immunosuppressive cytokine. Proposed mechanisms of anti-oxidant and anti-inflammatory activities in CRC inhibition as shown in Figure 1. Unpolished rice is claimed to inhibit CRC development and progression through the anti-oxidant and anti-inflammatory properties. It also induced cancer apoptosis by pro-oxidant function. However, the elucidated mechanisms are needed for further study to clarify the CRC carcinogenesis. Therefore, research targeting unpolished rice could be a promising approach for future therapeutic attempts in CRC treatment.

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