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REVIEW ARTICLE

Dietary alkylresorcinols and cancer prevention: a systematic review

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Abstract The potential role of alkylresorcinol compound from whole grains for prevention and inhibition of human cancer cell lines has been reported in observational and in vitro studies. The objective of this study was to present an updated review on the association between alkylresorcinols and cancer risk and aspects of their bioactivity with implications for carcinogenesis. Relevant studies were identified by searching PubMed, Scopus, ProQuest, EBSCOhost, SpringerLink, ArticleFirst, Taylor & Francis, Wiley Online, and ScienceDirect electronic databases using these search terms and key words: alkylresorcinols, cancer, carcinoma, risk. Furthermore, references from retrieved articles were also reviewed. Four observational and 10 in vitro studies were included in the analysis of natural or synthetic alkylresorcinols for anticancer activities. Two prospective studies reported a 52–66% risk reduction of distal colon cancer at nanomolar alkylresorcinols concentration in plasma; the remaining studies found no reduction of endometrial cancer risk and an approximate 40% increase in prostate cancer risk. In vitro studies presented inhibition of human colon, breast, lung, central nervous system, adenocarcinoma, hepatocarcinoma, cervix squamous carcinoma, and ovarian cancer cell lines, at micromolar alkylresorcinols concentration. Evidence from prospective studies confirmed significant inverse associations between whole grains intake and distal colon cancer risk. Model studies suggest a high cytotoxicity of alkylresorcinols toward cancer cells. These findings maintain that alkylresorcinols as components of whole grains are likely to find application in cancer prevention; however, the need for intervention studies to confirm their preventive action is warranted.

Keywords Alkylresorcinols · Bioactivity · Cancer · Prevention · Cytotoxicity

Abbreviations

ARs	Alkylresorcinols
ROS	Reactive oxygen species
IGF	Insulin growth factor
LDL	Low-density lipoprotein
ROO·	Peroxyl radical
FFQ	Food frequency questionnaire
IC_{50}	Inhibitory concentration–inhibit cellular proliferation by 50%
PSA	Prostate specific antigen
OR	Odds ratio
IRR	Incidence rate ratio
CI	Confidence interval
TGI	Concentration of drugs that totally inhibit cell growth
LC_{50}	Concentration of drugs resulting in cell death to 50%
5-AR	5-Alkylresorcinol
DNA	Deoxyribonucleic acid
ATP	Adenosine triphosphate

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Introduction

There are several environmental factors that influence cancer development. Studies demonstrate an independent effect of dietary patterns on cancer risk which are modifiable by diet. Evidence suggests that diet represents 30–35% of all risk factors contributing to the onset of cancer. Positive health effects have been reported for vegetables, fruits, and whole grains [1–6]. Whole grain foods, rich in dietary fiber, minerals, vitamins, and phytochemicals, are recognized as agents exerting health protective effects [7]. Much of the research on relationships between diet and cancer risk is based on the hypothesis that high intake of these nutrients rich in antioxidants (e.g., polyphenolic compounds, lignans, vitamins) may affect a number of physiological and pathological processes, like signaling mediated by MAP-kinases, insulin growth factor (IGF-1), nuclear transcription factor (NF-κβ), cytochrome P450, and reactive oxygen species (ROS) [8, 9]. Transformation of healthy cells and tumorigenesis can be linked to increased DNA mutagenesis, decreased apoptosis, increased cell proliferation, inflammation, and several other processes controlled by antioxidants, thus antioxidants can prevent DNA damage and potentially protect against cancer [10–13]. Nonetheless, the scientific evidence on diet–cancer risk interactions is not conclusive [5, 14]. Over the last two decades, research interest in medicine and functional food production in the application of whole grains and dietary phytoestrogens has increased significantly [1, 15]. Of particular interest in relation to tumorigenesis is the class of natural compounds, like phenolic lipids also known as alkylresorcinols (ARs) (Fig. 1).

A wide range of biological properties of ARs, including antimicrobial [16], antimutagenic [17], and antioxidant potency have been reported [7, 18]. Epidemiologic evidence demonstrates that consumption of whole grain cereals is associated with positive health benefits such as decreased risk of overweight and obesity, coronary heart disease, diabetes, and some types of cancer [19–24]. There is insufficient evidence to support the association of ARs with decreased risk of cancer because whole grains beside phenolic lipids contain a high number of primary metabolites (e.g., fiber, sulfur amino acids, lignin, oligosaccharides, minerals, vitamins), polyphenols (e.g., phenolic acids, flavonoids, lignans), phytosterols, melatonin, and other bioactive compounds [7, 15, 21, 25]. In addition, each of these compounds exhibits biological actions which are frequently reported in the literature as health protective mechanisms. In view of these facts, the main objective of this review article is to evaluate and present the current

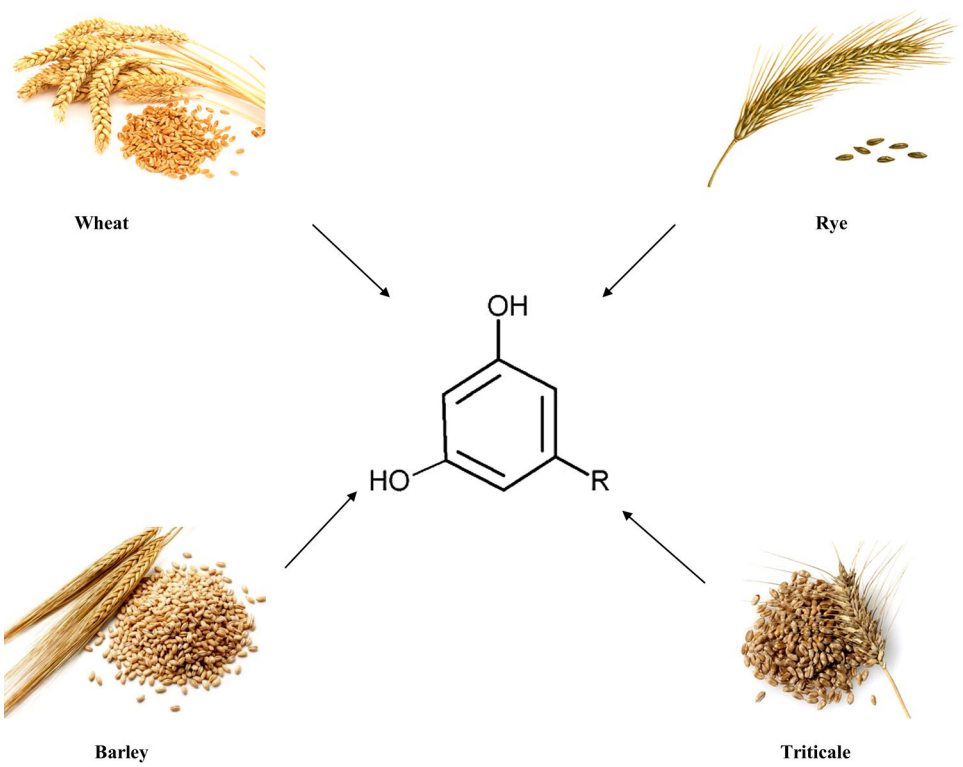

Fig. 1 General structure and common dietary sources of alkylresorcinols ($R = n$-alkyl or n-alkenyl chain)

evidence related to ARs and cancer risk and some aspects of the AR's biological activities related to carcinogenesis. Occurrence, pharmacokinetics, extraction, and analysis of ARs will be also presented briefly.

Methods

An integrative review of the literature was carried out prior to January 2017. Relevant articles were identified by applying search strategies to nine academic electronic databases: PubMed, Scopus, ProQuest, EBSCOhost, SpringerLink, ArticleFirst, Taylor & Francis, Wiley Online, and ScienceDirect. Search terms and key words included: Alkylresorcinols; cancer; carcinoma; risk. These databases were chosen due to their extensive coverage of biomedical and cross-disciplinary research objectives and scope. All retrieved titles, abstracts, and full-text publications were reviewed and screened for relevance to the topic. Furthermore, references from retrieved articles were reviewed to identify additional applicable publications.

Inclusion/exclusion criteria

Inclusion criteria for refereed study samples included observational and in vitro studies. Other article types such as conference abstracts, communications, commentaries, editorials, brief reports, position, and hypothesis-generating statements were excluded. Gray literature and non-refereed publications were also excluded. No language restrictions were imposed. A flowchart of the study screening and selection is presented in Fig. 2.

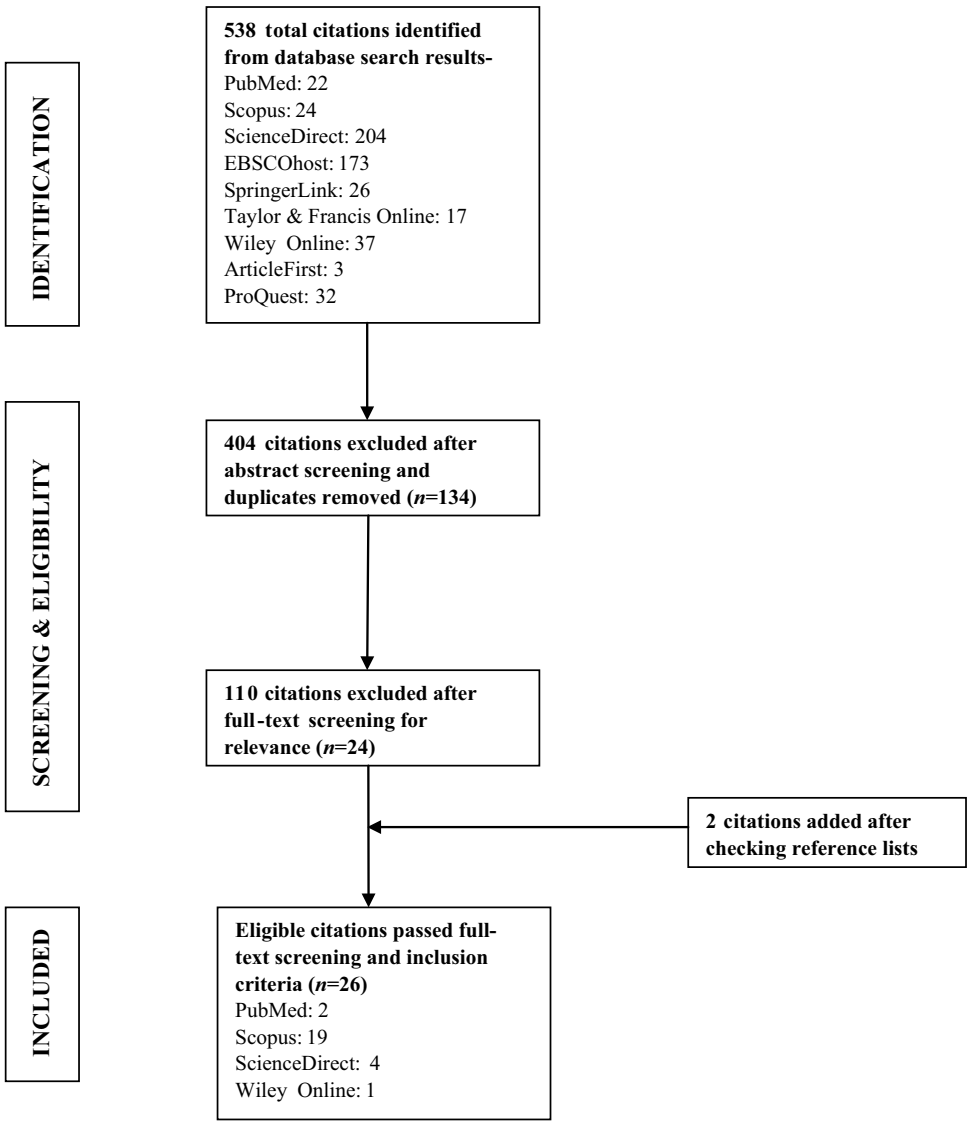

Fig. 2 Flow diagram of literature search process

Results

Prevalence of alkylresorcinols

This large group of phenolic compounds (1,3-dihydroxy-5-*n*-alkylbenzenes) (about 150 natural occurring ARs) [26] consists of a single phenolic ring with two hydroxyl groups (OH) in the meta-position and odd numbered alkyl side chain (R) which can contain between 13 and 27 carbon atoms with dominance in the range of C15–C25 at position 5C in the benzene ring [27]. The hydrocarbon chains can contain two double bonds between carbon atoms, ketone, or hydroxyl groups. The chemical structure and length of chains depend on biological origin [28]. The following five major classes of ARs have been reported in whole grain, wheat, and rye: 5-*n*-alkylresorcinols, 5-alkenylresorcinols, 5-oxoalkylresorcinols, 5-oxoalkenylresorcinols, and 5-hydroxyalkenylresorcinols [15]. Alkenylresorcinols, the phenolic lipids with unsaturated hydrocarbon side chains, accounted for about 20% of the total amount of ARs as were identified and quantified by Söderholm et al. in rye bread [29].

These compounds are present in several plant families and some bacteria, fungi, algae, and marine sponges [27]. Among food plants, ARs occur in the whole grain or bran fractions; they are distributed in the outer cuticula of the testa and inner cuticula of the pericarp in rye, wheat grains, and in smaller amounts in barley. Various cereal grains are grown in different countries, depending on climatic conditions. In the regions with cold temperature and poor quality soils, rye is an important cereal grain, although cultivation of rye constitutes just 3% of the worlds wheat production. The AR content, its chemical structure, and the homologue ratios differ between cereal grains and are dependent on several environmental factors like geographical region, soil composition, fertilization, and cultivation [30–32]. ARs occur mainly in the outer parts of whole wheat and rye products at high concentrations (200–4000 µg per gram of dry matter) and at low concentration in refined flour or products (40–280 µg per gram of dry matter) [33–35]. ARs are proposed as valid biomarkers of whole grain and rye consumption of cereal grains which are the main human food crop [30, 36–39]. The ARs concentration is dependent on grain type. For example, rye contains about 797–1231 µg/g of dry matter, wheat 220–650 µg/g of dry matter, and barley 40–110 µg/g of dry matter [40]. A relative high concentration (489–1429 µg/g of dry matter) of ARs occurs in wheat bran [15] of which human consumption has increased over the years [41]. Among cereal grains such as rye, wheat, and durum wheat, rye is richest in ARs [42].

Alkylresorcinols during grain processing

In contrast to whole grain foods, refined products contain only trace-concentrations of AR [15]. Grain processing (e.g., milling, cooking, fermentation) changes the nutritional content of cereal grains by fragmentation of the grain matrix and gelatinization of starch granules [7, 43]. Due to occurrence of ARs, vitamins, minerals and trace elements, and antioxidants in the outer parts of the grain, the final nutrient content will be dependent on the extent to which the outer parts are removed during processing. For example, refining whole grain wheat may result in the loss of about 58% of fiber, 79% of zinc, 79% of vitamin E, 83% of magnesium, and 92% of selenium [7]. High-temperature processing of cereal grains decreases AR content in grain food due to denaturation and degradation [15].

Anti-nutrients in grain cereals

Notably, whole grain cereals also contain anti-nutrients which exert both adverse and positive health effects [7, 44–46]. Anti-nutritional factors can reduce nutrient intake, design, absorption, and utilization. The factors are naturally present in grains or they originate from contamination (fungal origin, related to soil and other environmental influences). The most important are phytic acid, lectins, tannins, saponins, inhibitors of proteases, and amylases which modify the nutritional values of cereals. For example, tannins and the phosphorus compound phytic acid can bind iron, calcium, and zinc; lectins can damage the intestinal microvilli and interact with antibodies, thus stimulating an immune system response. There is significant interest in understanding how processing influences concentrations of bioactive phytochemicals present in whole rye, wheat, and barley from different cultivations and in obtaining functional ingredients rich in ARs [34, 47]. Therefore, several reduction strategies have been developed to reduce anti-nutrients and improve whole grain foods. For example, processing of cereal grains through cooking, roasting, fermentation, and germination may decrease concentration of tannins and phytic acid [3, 7].

Pharmacokinetics of alkylresorcinols

According to a scheme proposed by Landberg et al. [48], presenting the pathways of AR absorption, distribution, metabolism, and excretion, the compounds are absorbed in the small intestine, although there is no clear evidence describing the mechanism of absorption. The authors suggested that in the intestinal cells ARs can be assembled into chylomicrons, followed by their transportation into the lymphatic system. The compounds may also be absorbed

directly during transfer to HDL (high-density lipoprotein), LDL (low-density lipoprotein), and VLDL (very low-density lipoprotein) fractions. Next, from lipoproteins ARs are distributed into erythrocyte membranes, wherein the plasma-erythrocyte ratio is dependent on the chain length ranging from 0.5 to 1.3, being higher for longer homologues. An analysis of AR level in erythrocytes and in plasma showed that their concentration was maximal after about 13 h post-feeding (300–500 nM) and at 7 h (3365 nM), respectively when ARs are consumed several times daily. The ARs absorption level and elimination half-time, the time at which the excretion rate decreases to half of the maximal excretion rate in humans and animals, are the individual features changing at different value ranges between individuals [26]. Similar to tocopherols, ARs are eliminated from circulation with an apparent half-life about of 5 h [48]. These findings, as well as studies on metabolism of resorcinols and 4-n-nonylphenyl, propose similar metabolism of ARs as tocopherols including two phases. In phase I, ARs are metabolized by the introduction of a hydroxyl group (HO) at the end of the alkyl tail through omega-oxidation catalyzed by cytochrome P450 isoenzyme CYP4F2. Next, the HO group is oxidized to a carboxylic acid, followed by successive β-oxidation, thus making the alkyl chain shorted, and two main water-soluble metabolites: 3-(3,5-dihydroxyphenyl)-1-propanoic acid (DHPPA) and 3,5-dihydroxybenzoic acid (DHBA) are final products of this phase [42–48]. In phase II, ARs and their intermediate and final metabolites are partially conjugated by a polar group to xenobiotics or endogenous compounds. Conjugation with glucuronide sulfate groups and amino acids is the key reaction improving urinary excretion of AR metabolites. Two AR metabolites DHPPA and DHBA were detected in plasma and human urine [29, 49, 50] and considered as biomarkers of whole grain wheat and rye intake. For example, Söderholm et al. observed maximum exertion rates of 5–6 h for DHPPA and DHBA metabolites, and significant amounts were still measurable at 25 h in human urine [29]. Recently, new ARs metabolites 3,5-dihydroxycinnamic acid (DHCA), 5-(3,5-dihydroxyphenyl) pentanoic acid (DHPPTA), 3,5-dihydroxycinnamic acid amide (DHCA-amide), and 2-(3,5-dihydroxybenzamido)acetatic acid (DHBA-glycine) were developed in human urine samples [51, 52]. Although their concentrations in urine were considerably lower than those of DHPA and DHPPA metabolites [52], they are suggested as potential biomarkers for whole grain wheat and rye intake [51, 52].

Extraction and analysis of alkylresorcinols

For analytical studies, ARs require previous extraction and identification. The extraction process from cereal grains is important for accurate quantification of AR content in whole grain food products as they are potentially phytochemicals for use in disease prevention. Several methods including modern technologies have been applied to the extraction of ARs from plant material, mainly conventional solvent extraction, ultrasonic-assisted extraction (UAE), and subcritical fluid extraction (SFE) [15]. Briefly, the conventional extraction methods include Soxhlet extraction, stirring, distillation, manual mixing, and percolation. The extraction methods use refluxing samples with different organic solvents like acetone, ethylacetate, hexane, and propanol-water mixture (3:1) because ARs are insoluble or poorly soluble in water. Extraction methods are expensive and time consuming (1–48 h). SFE is a technique that uses a supercritical fluid as the extracting solvent and carbon dioxide (CO_2) is the most used supercritical fluid [53, 54]. The fluid is allowed to flow at a desired pressure of 40 MPa through a milled sample at an extracting temperature of 40–80 °C. The CO_2 fluid is often modified using ethanol or methanol to increase the extraction yield. The major advantage of SFE-CO_2 is high selectivity which shortens extraction time and lowers organic solvent costs compared to conventional extraction methods. Similarly, UAE is an efficient and inexpensive modern extraction technique of increased selectivity and kinetics. In UAE extraction, ultrasound is used to break the cell membranes. Diffusion of solvent through membranes is accelerated, thus the release of cell contents is facilitated [55]. It is worth noting that an important property of compounds containing phenol group, like antioxidant potential, may be influenced by the extraction solvent and extraction time [56]. However, no qualitative or quantitative differences in AR extradition were found after applying supercritical CO_2 and conventional extradition using ethyl acetate [57]. To determine the AR structure–activity relationship, synthetic compounds are prepared using Grignard and Wittig reactions [58]. Colorimetric methods, thin-layer chromatography, high-performance liquid chromatography, gas chromatography, mass spectrometry, and nuclear magnetic resonance are the techniques used for ARs separation, identification, structure establishment, and qualitative and quantitative analysis [15, 54, 59].

Biological activity of alkylresorcinols

ARs exhibit a wide range of biological properties due to their amphiphilic properties resulting from the presence of polar water-soluble OH groups attached to the benzene ring and the presence of a water-insoluble hydrocarbon chain. Current evidence for the biological importance of ARs is based mainly on in vitro examination. Three kinds of positive effects of whole grain cereals are identified: nutritional, mechanistic (due mainly to the fiber content), and antioxidant (due to ARs and phenolic acids) [39, 60].

Detections of ARs or their main metabolite concentration in blood plasma, erythrocytes, adipose tissue, and in urine are used to estimate whole cereal intake. Several studies reported positive correlations between whole grain intake and the presence of ARs in plasma or their urinary metabolites [36, 51, 61–69]. Finding of in vitro studies have shown that ARs exhibit a broad range of bioactivities including a high affinity to liposome and erythrocyte membranes increasing their permeability, antifungal, antimicrobial, and anticancer abilities [70–78]. ARs can potentially affect all processes regulated by enzymes; this suggests that ARs may exhibit anti-oxidative, anticancer, and antimutagenic activities, induction of apoptosis, and inhibition of some enzymes activities including lipoxygenases, monoamine oxidase, tyrosinase, Ca^{2+}-ATPase, α-glucosidase, dehydrogenase, DNA polymerase β, and lipase in the adipose tissue cells. ARs may also reduce adipose triglyceride, decrease copper-induced oxidation of LDL, inhibit DNA-strand scission, and limit nucleic and protein synthesis in thymocytes [42, 71, 72]. In vitro experiments show an inhibition of the human 20S chymotrypsin producing proteasome activities by several synthetic ARs and their homologues with a high potency. This human proteasome includes the catalytic core of a proteinase complex playing several important functions in cells such as controlling proteins p53, p27, and cyclin B levels and the ATP-dependent ubiquitin-mediated protein degradation [58].

Whole grains can improve insulin sensitivity due to their low glycaemic index [49]. Biskup et al. reported that only whole grain intake dominated by rye consumption may be important for type 2 diabetes mellitus prevention based on case-control study (931 cases, 931 controls) [65]. Ross et al. reported ARs can regulate with the high potency the γ-tocopherol and cholesterol concentrations in rat livers [79]. Further, the researchers found high doses of AR intake decreased excess hepatic lipids which can lead to hepatic insulin resistance and type 2 diabetes and increased concentrations of γ-tocopherol caused by slower metabolism [80]. In turn, a large population-based intervention study reported whole grain consumption is linked with decreased concentration of non-esterified fatty acids in plasma [36]. Also, Söderholm et al. found decreased peroxidation of LDL in the presence of copper ions in humans after 4 weeks of rye bread consumption [81]. Considering the antioxidant potential of ARs, it is worth noting that this activity is estimated at 10% of α-tocopherol antioxidant capacity, and the hydrogen donation ability of ARs corresponds to 30% of that exhibited by ferulic acid [36, 42, 82–85].

Some reports indicate weak direct antioxidant activities of ARs due to their hydrogen atom donor and free radical scavenging activities [60, 82, 83], but note a strong protective action in phospolipid bilayers, such as inhibition of linolenic acids oxidation and protection against H_2O_2-induced oxidation of erythrocytes [42]. The weak direct antioxidant power of ARs using the ferric reducing ability of plasma and DPPH assays was observed by Parrika et al. [82] who reported antioxidant activities of several ARs with chains lengths C15:0, C17:0, C19:0, C21:0, and C23:0 using the HT29 human colon cancer cells. ARs were found to increase the self-protection properties of these cells against DNA damage caused by H_2O_2 or genotoxic fecal water samples. Parrika et al. also observed a strong protective effect of these compounds against the Cu ion-induced oxidation of low-density lipids. Notably, lipid peroxidation is currently considered as the main biochemical mechanism involved in cell damage [13, 86]. Peroxidation of lipids is a chain reaction with repetitive H abstraction by hydroxyl radical and peroxyl radical. The main target is methylene group of polyunsaturated lipids. An addition of molecular oxygen (O_2) to the alkyl radicals resulting in generation of peroxyl radicals ($ROO^{\cdot}$) leads to their oxidative destruction [86]. The antioxidant property of ARs as polyphenolic compounds originates from the ability of their hydroxyl groups to donate H to a free radical, or to donate one electron to an alkyl free radical, which breaks the chain reaction of lipid peroxidation. Thus, ARs may modulate cellular redox state and protect proteins, phospholipids, DNA, RNA, and carbohydrates against peroxidation [82, 84, 85, 87].

There are no oral dosing studies that examine pure ARs in humans [38]. Only a few dietary clinical intervention trials have studied the effect of whole grains intake on health [20, 88–91]. For example, in a 12-week observational dietary intervention trial ($n = 79$), Kristensen et al. examined the effect of replacing refined wheat with whole grain wheat on body weight and percent body fat [90]. The outcome suggested intake of whole grain products may cause a greater reduction in fat mass percentage but was not associated with body weight change. Moreover, total and LDL cholesterol in serum was found to be increased in refined wheat consumers compared to whole grain wheat consumers (5.91 vs. 5.59 nM, $p = 0.02$ and 3.96 vs. 3.73 nM, $p = 0.02$, respectively). In turn, Tighe et al. found that daily intake of three portions of whole grain foods reduced cardiovascular disease in middle-aged people [89].

Prospective studies

Four observational studies [69, 92–94] were included in analysis of the association of ARs intake with cancer risk, among which two studies [92, 93] involved colorectal cancer. One study dealt with prostate cancer [69] and one study [94] with endometrial cancer (Table 1). The first study on colorectal cancer included a large, multicenter cohort with more than one million individuals from 10 European

Table 1 Characteristics of studies that investigated the association of alkylresorcinols and cancer risk

First author, study reference	Study design, *N*, sex	Type of measurement/specific cancer site/contrast	Effect on cancer incidence, relative risk (95% CI)	Adjustment for confounders
Kyrø et al. [92] European Prospective Investigation into Cancer and Nutrition	A nested case-control study; 1373 cases, 1373 controls in a cohort M/F	*Colorectal* cancer The highest *vs* the lowest quartile of plasma total ARs concentrations	*Decreased* risk of distal colon cancer IRR = 0.48 (0.28–0.83)	BMI, intake of red and processed meat, PA, smoking, education, alcohol intake
		Semi-reported food and lifestyle questionnaires	No effect for overall colorectal cancer, proximal colon cancer, and rectal cancer	
Knudsen et al. [93] HELGA cohort	A nested case-control study; 522 cases, 562 controls. The median follow-up period for cases was 4.6 years M/F	*Colorectal* cancer The highest *vs* the lowest quartile of plasma ARs concentrations	*Decreased* risk of distal colon cancer OR = 0.34 (0.13–0.92)	Age, sex, study center, time of blood collection, fasting status, additionally conditioned on menopausal status, HRT use or oral contraceptives for women
		Semi-reported food frequency questionnaires of whole grain intake	*No significant* association between ARs concentration in plasma and any colorectal cancers (colon, proximal, distal or rectum)	
Drake et al. [69] Diet and Cancer Study (MDC cohort); Malmö	A nested case-control study: 1016 cases, 1817 controls	*Prostate* cancer The highest (median 130.3 nM) versus moderate (median 44.1 nM) levels of ARs metabolites in plasma	*Increased* risk for high levels of ARs: OR = 1.41 (1.10–1.80)	Age, date of study entry, height, waist circumference, education level, smoking status, energy intake
		Low or higher *vs* moderate levels of AR metabolites in plasma	*Non-significantly* increased risk *Significant correlations* between ARs metabolites in plasma and whole grain intake. Observed evidence of a non-linear relation between ARs concentrations and cancer risk	
Olsen et al. [94] Danish "Diet, Cancer and Health" prospective cohort study; Copenhagen and Aarhus area	Nested case-cohort study, 177 cases, 152 sub-cohort members	*Endometrial* cancer The highest *vs* the lowest quartile of plasma concentration of individual or the total sum of AR homologs	*No significant association* between plasma levels of individual and the total sum of AR homologs and endometrial cancer risk	Parity, menopausal status, use of HRT, smoking status, use of estrogen, BMI

IRR incidence rate ratio, *OR* odd ratio, *CI* confidence interval, *M* males, *F* females, *BMI* body mass index, *HRT* hormone replacement therapy

countries [92]. Total plasma concentration defined as a sum of plasma AR homologues C17:0, C19:0, C21:0, C23:0, and C25:0 was analyzed in matched case-control pairs. The incidence rate ratio (IRR) of distal colon cancer was reduced by 52% among individuals with AR concentrations in plasma >99 nM in men and >84 nM in women (78 cases, 114 controls). Also, a 17% reduction in IRR of colon cancer was reported for Scandinavian participants (252 case-control pairs). The investigators noticed an inverse relationship between total plasma AR concentrations and colon and distal colon cancer which occurred only in individuals from areas where intake of ARs is high, stable, and frequent, i.e., in the Central Europe and Scandinavia.

The second study on the AR-colorectal cancer relationship examined levels of plasma AR homologues (C17:0, C19:0, C21:0, C23:0, and C25:0) and also used the food frequency questionnaire (FFQ) of whole grain intake [93]. The study included three cohorts: The Norwegian Women and Cancer Study, the Northern Sweden Health and Disease Study, and the Danish Diet, Cancer, and Health Study (a research project on Nordic health effects of whole grain consumption, HELGA). Approximately one hundred twenty thousand men and women aged 30–64 years experienced a 64% decreased risk of distal colon cancer (198 case–control pairs) reported after comparing the highest quartiles (>118.6 nM for men and >91.7 nM for women) with the lowest (≤35.3 nM for men and <27.5 nM for women) of AR plasma concentrations. Investigators suggested that usage of both assays, i.e., plasma ARs detection and FFQs of whole grains intake, slightly increases the precision of the study compared to a measure of the association whole grain products intake—cancer risk, using only an FFQ as the exposure measurement. This suggestion was based on finding no significant relationship between wholegrain intake and colorectal cancers when an FFQ was used as an assay.

Only one observational study [69] was identified and included in the comparative analysis between the highest and lowest levels of plasma AR metabolite concentrations and the risk of prostate cancer that estimated the dose–response (Table 1). The study analyzed prostate cases from the Swedish MDC cohort; the odds ratio among men was 1.41 (1.10–1.80) of which plasma AR metabolites concentrations ranged from 93.0 to 596.2 nM (226 cases) compared to those which plasma AR metabolites concentration ranging from 34.1 to 55.8 nM (179 cases). A slightly higher significant risk was found for low-risk prostate cancer (46%); although the positive association between AR metabolite concentrations and prostate cancer risk had no linear shape. Interestingly, the positive associations of fiber and whole grain intake with prostate cancer was found by Nimptsch et al. in the Health Professionals Follow-up Study (hazard ratios, HR = 1.13; 95% CI = 1.03–1.24, 49,934 cases) which lacks statistical importance after restriction to PSA screening [95]. Investigators also observed non-significant increased ORs among 647 cases with low risk of prostate cancer and 353 cases with high risk, and for 465 cases with symptomatic prostate cancer. Further, significant moderate correlations between AR metabolites and whole grain products intake were found. The results from this study led investigators to conclude high whole grain intake does not reduce risk of prostate cancer.

A case-control study of the Danish postmenopausal women aged between 53–60 years including 177 endometrial cancer cases and 152 sub-cohort members as a control group evaluated concentrations of AR homologues (C17:0–C25:0) in their plasma [94]. Median AR concentration of 78 nM and a lack of statistically important differences between cases and controls with regard to the AR concentration in plasma were found. Investigators confirmed that rye bread consumption was the primary determinant of AR levels and elevation of plasma AR concentrations in non-fasting blood samples. A group of 360 postmenopausal Danish women had the same level of ARs for the joined controls and endometrial cancer cases ($n = 176$) [62].

Cytotoxic activities of alkylresorcinols

Ten in vitro studies [58, 84, 96–103] were identified and included in the analysis of natural and synthetic ARs for activities that inhibit growth of human cancer cells (Table 2). The studies focused on isolation and identification of naturally occurring ARs and their synthesis. Two studies [58, 96] reported isolation of ARs from wheat bran, a synthesis of several dozens of ARs and their evaluation for growth inhibitory potential against human colon cancer cell lines HCT-116 and HT-29, when treated with various concentration of ARs extracted from wheat bran oil [96]. Investigators examined a series of ARs having different site chain lengths (synthetic including those of short to moderate length side chain: C9:0, C11:0, C13:0, C15:0, C17:0 [58] and those isolated from wheat bran oil: C17:0–C25:0) [96] (see Table 2). The inhibitory effect on the colon cell lines growth was reported as an IC_{50} (the half maximal inhibitory concentration as a measure of the activity of AR in inhibiting cancer cell growth). The observed cytotoxic effect was dependent on chemical structure of ARs, being weaker for the compounds with the longer alkyl site chain ($C > 17$) and dependent on type of colon cancer cells HCT-116 or HT-29, with IC_{50} values about 15 μM (C13:0 and C15:0) and approximately 25 μM for compounds C:13 and C15:0, respectively [58]. ARs C13:0 and C15:0 were the most effective as colon cancer cell growth inhibitors, and hydroxyl groups in meta-position at C1 and C3 on the aromatic ring played an important role in inhibition of cancer cell growth. Investigators also found wheat bran

Table 2 The cytotoxic activity of alkylresorcinols on cancer cell lines

References	Model system	Alkylresorcinols/concentration	Activity/effect
Zhu et al. [58]	Human colon cancer cell lines HT-29 and HTC-116	Fifteen synthetic ARs including five of short to moderate length side chain (C9:0, C11:0, C13:0, C15:0, C17:0) Concentration range: 0–50 μM	Inhibition of cell lines by ARs having short to moderate length side chain. HT-29: IC_{50} values ranging between 24.86 and >50 μM; HCT-116: IC_{50} values ranging between 14.84 and 53.10 μM. Other test ARs showed IC_{50} values above 100 μM Observed the greatest inhibitory effects in both colon cancer cells lines for ARs C13:0 and C15:0, which decreased with increasing or decreasing the side chain lengths
Zhu et al. [96]	Human colon cancer cell lines HT-29 and HTC-116	Thirteen ARs from wheat bran oil: C17:0-C25:0 Concentration range: 5–50 mg/L	Inhibition of both colon cancer tumors growth: HT-29:IC_{50} values ranging between 81.1 and >108.4 μM, HTC-116:IC_{50} values ranging between 47.5 and >108.4 μM Inhibition was dependent on chemical structure of ARs; the longer alkyl side chain the weaker inhibition; the presence of a double bond and a carbonyl group caused an increase of inhibition
Sánchez et al. [97]	Human breast (MCF-7), lung (H-460), central nervous system (SF-268) human cancer cell lines	Five ARs isolated from the leaves of *Homalomena wendlandii Schott* (*Araceae*)	Inhibition of all cancer tumors growth: MCF-7:IC_{50} values ranging between 8.24 and >42.17 μM; H-460:IC_{50} values ranging between 10.02 and >42.17 μM; SF-268:IC_{50} values ranging between 14.53 and >42.17 μM The cytotoxic effects on cancer cells of ARs were at least 8.0, 9.5, and 13.8 times lower compared to the positive control adriamycin, respectively
Chuang and Wu [98]	Human breast (MCF-7), lung (H-460), central nervous system (SF-268) human cancer lines	Fourteen ARs compounds isolated from the leaves of *Grevillea robusta* as pure compounds	Inhibition of all tested cancer tumors growth: MCF-7:IC_{50} values ranging between 28.6 and 37.1 μM; NCI-H460:IC_{50} values ranging between 22.8 and 35.4 μM; SF-268: IC_{50} values ranging between 27.7 and 39.8 μM
Liu et al. [99]	Human prostate adenocarcinoma (PC3) cell line from the European Collection of Cell Culture	ARs with long chain (≥C17:0) alkenyl—and oxoalkyl—resorcinols (seven pure compounds isolated from wheat bran) Concentration range: 25–200 mg/L	All examined ARs exerted the cytotoxic effect on the PC3 cell line. IC_{50} values ranging between 24.4 and >531.9 μM Four of the seven tested ARs were more active against the cancer cell line (IC_{50} values ranging from 24.4 to 105.0 μM) compared to the positive control chlorambucil (IC_{50} = 192.9 μM)
Barbini et al. [84]	Human hepatocarcinoma cell lines, HepG2 and Hep3B	5-alkylresorcinol isolated from *Lithraea molleoides* Concentration range 1–4 mg/L	Inhibition of cancer cells growth: HepG2: IC_{50} = 45.49 μM; Hep3B: IC_{50} = 43.17 μM The effects on cellular morphology, such as DNA fragmentation characteristic of apoptosis, fragmentation and condensation of nuclei have been reported

Table 2 continued

References	Model system	Alkylresorcinols/concentration	Activity/effect
Chaturvedula et al. [100]	Human ovarian A2780 cancer cell line	Ten 5-ARs isolated from the leaves of *Oncostemon bojerianum A*. from the uriname and Madagascar rainforests	Inhibitory effect; IC_{50} values ranging between 17.89 and 22.92 μM
Al-Mkhlafi et al. [101]	Human prostate (PC-3), colon (HCT-116), and breast (MCF-7) cancer cell lines	Several ARs isolated from leaves of *Labisia pumila* (Myrsinaceae) were evaluated for cytotoxic activity at concentration of 10 μM against MCF-7 breast cancer cells. Next, the ARs causing >50% cell death were tested at concentrations ranging from 0.1 to 100 μM to obtain IC_{50}, TGI, and LC_{50} parameters	Compounds 1–0-methyl-6-acetoxy-5-(pentadec-10Z-enyl) resorcinol and acetoxyresorcinol 1–0-methyl-6-acetoxy-5-pentadecylresorcinol exhibited sub-micromolar to low micromolar growth inhibitory activities for the tested cancer cell lines: IC_{50} values ranging from 0.3 to 0.5 μM, TGI—from 1.0 to 15.0 μM, and LC_{50}-from 7.7 to 41.3 μM. The authors observed the cancer-type selectivity against PC-3 and HCT-116 cells at the TGI and LC_{50} concentrations. TGI and LC_{50} values were lower in PC-3 and HCT-116 cells than in MCF-7 cells indicating lower sensitivity of the MCF-7 cells. The cytotoxic power of these two ARs was higher than anticancer drug doxorubicin at the IC_{50} level
Kubo et al. [102]	Human breast cancer cell lines BT-20 Human cervical cancer cell lines HeLa	Four cardols (5-alkylresorcinols) and four methyl-cardols isolated from the cashew nut and nut shell oil	All examined cardols exhibited significant cytotoxicity against both cancer cell lines. For BT-20 lines IC_{50} values ranging between 5.40 and 19.51 μM. For HeLa lines IC_{50} values ranged between 8.15 and 12.5 μM. All tested compounds had a C15:0 alkyl side chain with up to three double bonds
Vila-Luna et al. [103]	Human ceruix adenocarcinoma (HeLa), cervix squamous carcinoma (SiHa), breast cancer adenocarcinoma (MCF-7), prostate adenocarcinoma (DU-145) cell lines	Two ARs, (3-methoxy-5-octylphenol and 3-methoxy-2-methyl-5-pentylphenol) isolated from *Bonellia macrocarpa* roots	Both ARs exhibited low cytotoxic activity against all tested cancer cell lines (IC_{50} (μM): HeLa—308.24, 233.83; SiHa—154.8, 107.04; MCF-7—262.56, 184.34; DU-145—195.32, 130.15 for 3-methoxy-5-octylphenol and 3-methoxy-2-methyl-5-pentylphenol, respectively) as compared to docetaxel activity (0.25, 0.22, 0.01 and 0.01, respectively). The compounds exhibited better cytotoxic activity than antiproliferative activity in all tested cell lines (IC_{50} (μM): 577, 490; 262, 353; 356, 304; 590, 222 μM, respectively)

IC_{50}—the 50% inhibitory concentration of AR for treated cancer cells; TGI—the concentration of the compounds that totally inhibits cell growth; LC_{50}—the concentration of the compounds that results in death to 50% of cells

oil fractions containing 5-*n*-alk(en)ylresorcinols exerted the strongest inhibitory effect on the proliferation of human colon cancer cells [96], however their ability to inhibit colon cancer cell lines was lower than synthetic ARs.

In other research, ARs were responsible for the inhibition of human breast, lung, and central nervous system cancer cell growth [97]. The compounds cytotoxicity toward cancer have been presented on MCF-7, H-460, and SF-268 cell lines using five isolated natural ARs. Importantly, the isolated ARs exhibited at least an 800% stronger inhibitory effect on the tested cancer cell lines than the commonly known cytostatic adriamycin. This study confirmed the findings of Zhu et al. [96] that free phenolic hydroxyl groups of ARs play important role in anticancer action. These findings confirmed also previously published evidence on an inhibitory effect of 14 ARs isolated from leaves of a tropical ornamental tree on human breast carcinoma, lung carcinoma, and central nervous system carcinoma cells [98]. This study observed slightly lower IC_{50} values in the human lung tumor cell line (NCI-H460) compared to the human breast tumor and human central nervous system cancer cell lines. Investigators suggested the comparable values of IC_{50}, obtained during the cytotoxic evaluation of ARs, can attest that the alkyl chain structure (straight or cyclic) has no effect on cancer cell inhibition. In turn, a study by Liu et al. confirmed in vitro anticancer effects of ARs using human prostate adenocarcinoma (PC3) cells [99]. Liu et al. isolated seven pure ARs from wheat bran and four exhibited strong inhibitory capacity against the growth of PC3 cells; the latter compounds C17:0, C19:1, C21:1, and C23:0xo were the minor ARs with low yield in the isolation process. In conclusion, Liu et al. suggested their results are the first in the literature showing the cytotoxicity of ARs with a longer chain than C17:0 isolated from wheat bran.

Another study demonstrated the cytotoxic effect of 5-alkylresorcinol (5-AR) isolated from *L. molleoides* leaves in the human hepatocarcinoma cell lines HepG2 and Hep3B [84]. Treatment of both cell lines with 5-AR for 24 h resulted in induction apoptosis, DNA fragmentation, and nuclear condensation. Cell death observed in both cell lines tested included AR concentration-dependent where IC_{50} values found for HepG2 and Hep3B were similar. Investigators indicated an important property of 5-AR as of an inductor of apoptosis independently on a p53 pathway (p53 gene is the most commonly mutated gene in hepatocellular cancer). The ability of ARs to inhibit the growth of ovarian cancer cells has been reported by Chaturvedula et al. [100]. Effects of eight new 5-ARs isolated from leaves of *Myrsinaceae* and two known early ARs on the A2780 mammalian ovarian cancer cell line were examined. All compounds inhibited the growth of the cell line; the inhibitory effect was concentration-dependent, and IC_{50} values were comparable (17.89–22.92 μM). This finding suggests the tested compounds exhibited similar activity toward the cancer cells and, according to the researchers, the activity depends mainly on the basic skeleton of the 5-ARs.

The ability of ARs to inhibit the growth of prostate, colon, and breast cancer cells has been confirmed by Al-Meklafi et al. [101]. Twelve isolated ARs from an important medicinal herb in Malaysia were tested and two ARs (structurally very closely related) exhibited the most cytotoxic activity against PC-3, HCT-116, and MCF-7 human cancer cell lines, and were more active than doxorubicin at the IC_{50} level. The compounds showed cancer cell-type selectivity against PC-3 and HCT-116 cells at concentration which totally inhibits cell growth and concentration which results in cell death of up to 50%. Both compounds had a substituted aromatic ring by hydroxyl, methoxyl, and acetyl groups and C15:0 alkyl or alkenyl side chain with one double bond. According to Al-Meklafi et al., the presence of the double bond had no effect on the compound cytotoxic activity [101].

The studies of Sánchez et al. [97], Chuang and Wu [98], and Al-Mekhlafi et al. [101] confirmed the findings of Kubo et al. [102] on cytotoxicity of ARs against human breast cancer cell lines. Kubo et al. found that ARs and their methyl derivatives also exhibited significant cytotoxicity against human cervical cancer cell lines HeLa. Also, a study by Vila-Luna et al. [103] observed the cytotoxic effect of two phenolic lipids isolated from roots of *B. macrocarpa* against several human cancer cell lines including cervix (HeLa, SiHa), breast (MCF-7), and prostate (DU-145).

Discussion

This review article focuses on a relatively new research area because AR benefits have attracted significant interest in the last two decades. Evidence from different model studies show ARs are phenolic lipids abundant in several plant families, some bacteria, fungi, algae, and marine sponge, mainly as homologues with alkyl chains (C15:0–C25:0), though many studies examined derivatives having unsaturated and oxygenated side chains. Dietary ARs are easily absorbed by humans and several studies focused on their detection in blood plasma, adipose tissue, erythrocytes, and their metabolites in urine. Evidence has demonstrated that AR content or their metabolites in humans is proportional to intake of food products containing whole grains. Thus, there is rich evidence on usefulness of plasma and urine AR metabolite measurements as biomarkers of whole grain food, mainly whole grain wheat and rye consumption [37, 38, 42, 46, 47, 49, 62, 65, 67]. Studies which analyzed AR occurrence, absorption, metabolism, and excretion reported

their presence at micromolar concentration in plasma being the highest after cereal grain intake and at nanomolar concentrations at fasting conditions. All studies confirmed that a refining process leaves only trace amounts of ARs in food products. Phenolic compounds like ARs can potentially affect a number of physiological and pathological processes related to metabolism and immune system functions [71, 72, 104–111].

Results of model studies indicated that ARs which can affect all cellular processes regulated by enzymes, affect genotoxicity, suppress an adipocyte lipolisis, have a high affinity to erythrocyte membranes, exert indirect antioxidant activity, and have cytotoxic effects on cancer cell lines [58, 80, 82, 96–99, 103, 105, 112, 113]. Evidence for AR bioactivity in vivo is limited to a few dietary clinical intervention trials which examined the effect of whole grains intake [88–90, 114]. The majority of studies highlight cereal grains as an important source of many other bioactive compounds, such as benzoxazinoids, lingnans, phenolic acids, tocols, and phytosterols that are known to reduce cancer in humans, as recently reviewed [1, 15, 19, 37, 73, 74, 114–116].

Results based on two case-control studies of lower distal colon cancer risk with high plasma AR concentrations (Table 1) are consistent with a meta-analysis of six prospective and nested case-control studies which reported the reduced summary relative risk of colorectal cancer after three servings daily of whole grains (RR = 0.83) [5]. Also noteworthy, the latest systematic review of 12 studies on cancer mortality with 34,797 deaths related to whole grain intake (3 studies) or whole grains product intake (9 studies) found a dose-dependent reduced risk of cancer mortality (RR = 0.82) [107]. Analysis showed that men with high concentrations of AR metabolites in plasma had increased prostate cancer risk. In turn, a lack of risk reduction was observed in case of endometrial cancer. These findings are consistent with evidence from in vitro studies with regard to colon cancer but not prostate cancer (Table 2). In vitro evidence showed inhibition of colon, breast, lung, and central nervous system human cancer cell growth, and the ARs cytotoxicity against the prostate adenocarcinoma, hepatocarcinoma, cervix adenocarcinoma, cervix squamous carcinoma, and ovarian cancer cell lines. We noticed that the chain length of ARs was important for the ARs ability to inhibit cancer growth, with shorter chains like C13:0, C15:0, and C17:0 appearing to have the highest potency of cancer inhibition which is in line with previous findings [105]. Long chain ARs may be absorbed to a lesser extent compared to the shorter-chain homologs. The listed IC_{50} values in Table 2 allow us to suggest high levels of ARs appeared to be toxic to cancer cells. These findings are consistent with evidence from the model studies which reported a lack toxicity of ARs of moderate concentration, i.e., of 5–20 μM toward to healthy HepG2 or 3T3-L1 cells [42, 107, 113].

The observed differences between findings reported in Tables 1 and 2 may be explained by a relative short half-life time (~4–5 h) limiting the precision of plasma AR concentration detection, especially in populations in which food rich in rye and whole grain components is not consumed daily [93], although Landberg et al. reported a high correlation coefficient between plasma AR concentration and whole grain wheat and rye intake during a 6-week intervention study [35]. There are several hypothesized mechanisms by which ARs can exert inhibition of cancer risk, although the mechanisms do not consider the possible interaction and synergy between the functional components of a diet, like phenolic compounds, fiber, lignans, phytosterols, and vitamins, which are reported to exhibit beneficial effects on human health including cancer prevention [15, 23, 37, 46]. These potential interactions need to be verified with further research.

In vitro studies revealed the dose–response cytotoxicity of ARs toward many cancer cell lines is due to their strong effect on cellular morphology, such as DNA fragmentation and nuclear condensation, among others; this action can lead to apoptosis [84]. Increase in p53 concentration plays a key role in the expression of pro-apoptotic proteins [104]. The apoptotic pathway has been confirmed by Barbini et al. who observed an induction of apoptosis by 5AR in HepG2 and Hep3B cells [84]. The group further underlined an important feature of 5-AR for hepatocellular carcinoma therapy, i.e., its ability to trigger apoptosis independently on p53 or Fas phenotypic profile as they observed in Hep3B cells. Also, other research groups have maintained the anticancer effects of ARs are explained by enhancing apoptosis in genotoxically damaged lymphocytes [72]. Some studies provide insight to the ARs structure-dependent relationship finding an important role of free hydroxyl, methoxyl, acetyl, or methyl groups on benzene rings for observed cytotoxicity [98, 102, 103]. For example, the comparable IC_{50} values observed in cytotoxicity of 14 pure 5-ARs by Chuang and Wu [98] were partially explained by their antioxidant properties due to scavenging reactive oxygen species and/or inhibition of enzymes involved in the formation of free radicals under physiological conditions [70]. Alkylresorcinols contain two hydroxyl groups placed in meta-position of the phenolic ring, thus they have a week direct antioxidant potency. However, under alkaline conditions and in the presence of transition metal ions, e.g., Cu and Fe, ARs may be converted to trihydroxyalkylbenzenes—the compounds of a high antioxidant activity able to produce superoxide anion radicals and further hydrogen peroxide and hydroxyl radicals which can damage DNA, proteins, and lipids [72, 106, 108]. Moreover, the next important reported property of ARs that may also be

clinically significant is a slower metabolism of these compounds under pathological conditions [67].

Results from this study agree with findings of RCTs which demonstrated that participants receiving whole grain interventions had reduced fasting concentrations of insulin and glucose and reduced levels of total and LDL cholesterols, among other potential benefits which can be important for reduction of inflammation and certain cancers protection, as reviewed by Ye et al. [78]. The evidence for the potential role of whole grain food intake for general health benefits and mortality prevention [107] recommends increased consumption of whole grain cereal food products in most countries [117–119]. According to an expert panel report on dietary recommendations [120], at least 8 g of whole grains per about 30 g, without a fiber, (or at least 51% of total weight as whole grain content) is required as a minimum content of whole grains food. The recommended quantities of daily whole grain cereal product consumption vary considerably between countries [7, 120]. For example, at least three servings per day, i.e., approximately 48 g per day of whole grain cereals, are recommended in USA; three to eight servings per day of grain products at least one-half of them contain whole grains in Canada, at least 50 g per day of coarse grains including whole grains in China [120]. In the Scandinavian countries, at least 75 g of whole grain cereals intake per 10 MJ of total energy intake is recommended [40]. Of note, the reported dietary whole grains guidelines are much higher than their average daily consumption (e.g., 42 g per day in Sweden, 36 g per day in Denmark). A study by Piironen et al. reported the beneficial influence of whole grains may result from the combined action of fiber, vitamins, phenolic acid, ARs, micronutrients, and other phytochemicals [121]. This suggestion originates from observations that no single antioxidant can replace natural phytochemicals in preventing disease [122]. According to Fardet, there is agreement that the protective effect of whole grain cereals results from the synergistic action of phytochemicals and micronutrients occurring mainly in the bran and germ fractions [7]. To our knowledge, the synergy between phytochemicals present in whole grain cereal products is still not confirmed, due to their huge number and numerous biological functions. However, the evidence on an association of the whole grains consumption and decreased cancer risk is still inconclusive.

Limitations of the study

When assessing the relationship between AR concentrations and cancer risk, several methodological issues need to be considered. Two of the four analyzed observational studies used semi-reported food frequency questionnaires to assess whole grains intake which is prone to measurement errors in evaluation of associations between dietary intake and risk of civilization diseases [35, 117, 119, 123]. The errors originate from a positive difference between studies in distinct definition of whole grains, a lack of full food composition, large differences of AR concentrations in whole grain products, variation in AR concentration with time or a dependence of a half-time on the chain length, and variability across studies of serving size. Next, not all observational studies included a list of potential confounders, such as physical activity, fruits, vegetables or red meat intake, ethnicity, and family history of cancer. These variables, which are lacking in the statistical models, might lead to under- or over-estimation of the AR intake/cancer relationship [4, 6, 112, 124–129]. For example, physical activity is considered as an important lifestyle component, of which the association with colorectal cancer risk has been established as *conclusive*, and with the postmenopausal breast cancer as *probable* [127, 130]. Moreover, a higher intake of whole grains is usually reported by individuals of healthier lifestyle behaviors, thus all components of lifestyle should be included in statistical analyses as important confounders. Also, some limitations should be acknowledged when interpreting the findings from in vitro studies. The assessment of AR cytotoxicity toward human cancer cell lines may be underestimated because phenolic lipid content and antioxidant activity of plant extracts largely depend on extraction conditions and solvent polarity [56]. Due to fermentation processes, the release of ARs in vivo may be more effective than under in vitro conditions. Furthermore, bioactivity of isolated or synthesized ARs can decline during isolation and storage undergoing oxidation. Also, different methods of processing influence AR concentration in a food. Plasma concentrations of ARs are also influenced by differences in individual absorption and/or metabolism rates. Next, the association of ARs with cancer may by dependent on embryologic origins, on kinds of cancer or subtypes, as seen in observational findings with colorectal cancer (Table 1). Moreover, different sensitivity levels for detection of ARs in biological samples might introduce measurement errors which could explain relatively low AR concentrations in plasma. Finally, misclassification of an outcome when FFQs are used is also probable because ARs are considered in the literature as biomarkers of whole grain wheat and rye intake, only [92]. A correction for measurement errors can enhance the reported associations and weaken the discrepancy between the findings of observational and in vitro studies.

Conclusions

This systematic review demonstrated a renewed interest in the beneficial effect of ARs on human health. Evidence

indicates that ARs exhibit a variety of bioactivities; they can affect many physiological and pathological processes related to the immune system, being involved in cell signaling and gene regulation. These findings originate mainly from model and epidemiological studies where assessment of the AR bioactivity in vivo is limited to a few dietary clinical intervention trials. ARs characteristic feature is their potential as biomarkers of whole grain wheat and rye product consumption. There is evidence that individuals with high plasma AR concentrations had above 52% reduced risk of distal colon cancer with linear dependence originating from biomarker concentration and indirectly from whole grain intake. These findings show that the accuracy of epidemiological studies of whole grain intake and cancer risk based on FFQs may by increased by detection of AR concentration in plasma. In vitro studies show that high-concentration ARs are considered highly cytotoxic agents for certain types of cancer, reporting inhibition of human colon, breast, lung, central nervous, ovarian, cervical, and prostate tumors, and hepatocarcinoma cancer cell lines. Furthermore, the phenolic ring and alkyl chain are important for inhibition of human cancer cells proliferation. This is no common consensus or clarity on the toxicity mechanism toward cancer cells due to multiple AR targets and the complexity of interrelations between various biochemical actions. Observational studies help to evaluate relationships between AR intake and beneficial health effects yet cannot be used to establish causality when compared to intervention studies. The research literature has generated several hypothesized molecular mechanisms of action for ARs in the prevention of cancer and their cytotoxic activities which include the ability to affect all cellular processes regulated by enzymes, suppress an adipocyte lipolysis, affect genotoxicity, have a high affinity to erythrocyte membranes, and exert indirect antioxidant capacity.

Our findings provide further support for public health recommendations emphasizing diets rich in whole grains as potentially preventive against some types of cancer. The updated evidence suggests future studies should focus on identification of a fraction from grain cereals containing concentrations of ARs exerting the strongest cytotoxic effect on cancer cells; this may offer new clues to prevent cancer.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Compliance with ethics requirements This article does not contain any studies with human or animal subjects.

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