Quimiopreventive Action of Phytochemicals through Regulation of Transcription Factor Nrf2: Integrative Literature Review

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Ação Quimiopreventiva dos Fitoquímicos por meio da Regulação do Fator de Transcrição Nrf2: Revisão Integrativa da Literatura

Acción Quimiopreventiva de los Fitoquímicos a través de la Regulación del Factor de Transcripción Nrf2: Revisión Integradora de la Literatura

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Abstract

Introduction: The nuclear factor erythroid 2-related factor 2 (NRF2) plays a fundamental role in the expression of genes mediated by antioxidant response element (ARE), thus it is an important pathway to protect the cells from carcinogenic substances. **Objective**: To perform an integrative literature review on the quimiopreventive action of phytochemicals through regulation of the transcription factor Nrf2. **Method**: Search of papers for the integrative literature review about this theme conducted in journals indexed in the databases: Academic Google, PubMed, SciELO, ScienceDirect and Springer Link, using the MeSH descriptors: phytochemicals, free radicals, oxidative stress, carcinogenesis, chemoprevention and Nrf2. The selection criteria were articles published from 2000 to 2019, related to or that directly investigate the role of phytochemicals in the transcription factor Nrf2, and the prevention of cancer development. **Results**: 58 articles were selected, all related to the objective of the review. The reviewed studies showed that phytochemicals, such as resveratrol, curcumin, isothiocyanate, luteolin, among others, act on the activation of the Nrf2 pathway, using different mechanisms, which are dependent or independent of the repressor protein *Kelch-Like Epichlorohydrin-Associated Protein 1*. **Conclusion**: Therefore, the conclusion is that the modulation of the transcription factor Nrf2 is a mechanism that configures itself as an important mediator for harmful compounds to the human organism, and that the action of phytochemicals, in this pathway, contributes to the reduction of cancer risk. However, all the mechanisms used by phytochemicals, are not completely elucidated, and further studies are needed in the area.

Key words: Antioxidants; Carcinogenesis; Oxidative Stress; Free Radicals; Review.

Resumo

Introdução: O fator nuclear eritroide 2 relacionado ao fator 2 (Nrf2) desempenha papel fundamental na expressão de genes mediados por elemento de resposta antioxidante (ERA); sendo assim, é uma via importante para proteger as células de substâncias carcinogênicas. **Objetivo**: Realizar uma revisão integrativa da literatura acerca da ação quimiopreventiva dos fitoquímicos por meio da regulação do fator de transcrição Nrf2. **Método**: O levantamento de artigos para a revisão integrativa da literatura sobre essa temática foi realizado nos periódicos indexados nas bases de dados: Google Acadêmico, PubMed, SciELO, *ScienceDirect* e *SpringerLink*, utilizando-se os descritores advindos do *MeSH*: fitoquímicos, radicais livres, estresse oxidativo, carcinogênese, quimioprevenção e Nrf2. Os critérios de seleção foram artigos publicados de 2000 a 2019, relacionados, ou que investiguem diretamente a atuação de fitoquímicos no fator de transcrição Nrf2, e a prevenção do desenvolvimento de câncer. **Resultados**: Foram selecionados 58 artigos que estavam relacionados com o objetivo da revisão. Os estudos revisados apontaram que fitoquímicos, tais como resveratrol, curcumina, isotiocianato, luteolina, entre outros, atuam na ativação da via Nrf2, utilizando diferentes mecanismos, sendo eles dependentes ou independentes da proteína repressora *Kelch-Like Epichlorohydrin-Associated Protein 1*. **Conclusão**: Diante disso, conclui-se que a modulação do fator de transcrição Nrf2 é um mecanismo que se configura como um importante mediador no que concerne compostos nocivos ao organismo humano, e que a atuação dos fitoquímicos nessa via contribui para a redução do risco de câncer. No entanto, ainda não são completamente elucidados todos os mecanismos utilizados pelos fitoquímicos, sendo necessários ulteriores estudos na área.

Palavras-chave: Antioxidantes; Carcinogênese; Estresse Oxidativo; Radicais Livres; Revisão.

Resumen

Introducción: El factor nuclear eritroide 2 relacionado con el factor 2 (Nrf2) desenvuelve un papel fundamental en la expresión de los genes mediados por él elemento de respuesta antioxidante (ERA), por lo tanto, es una vía importante para proteger las células de las sustancias carcinógenas. **Objetivo**: Realizar una revisión integradora de la literatura sobre la acción quimiopreventiva de los fitoquímicos mediante la regulación del factor de transcripción Nrf2. **Método**: El levantamiento de artículos para la revisión integral de la literatura sobre este tema se realizó en revistas indexadas en las bases de datos: Google Académico, PubMed, Scielo, *ScienceDirect* y *SpringerLink*, usando los descriptores MeSH: fitoquímicos, radicales libres, estrés oxidativo, carcinogénesis, quimioprevención y Nrf2. Los criterios de selección fueron artículos publicados entre 2000 y 2019, relacionados o que investigan directamente el papel de los fitoquímicos en el factor de transcripción Nrf2 y la prevención del desarrollo del cáncer. **Resultados**: 58 artículos relacionados con el objetivo de la revisión fueron seleccionados. Los estudios revisados mostraron que los fitoquímicos, como el resveratrol, la curcumina, el isotiocito, la luteolina, entre otros, actúan sobre la activación de la vía Nrf2, utilizando diferentes mecanismos, que son dependientes o independientes de la proteína represora *Kelch-Like Epichlorohydrin-Associated Protein 1*. **Conclusión**: Por lo tanto, se concluí que la modulación del factor de transcripción Nrf2 es un mecanismo que se configura como un importante mediador en relación con los compuestos nocivos para el cuerpo humano, y que la acción de los fitoquímicos en esta vía contribuye a reducir el riesgo de cáncer. Sin embargo, todos los mecanismos utilizados por los fitoquímicos aún no se han dilucidado por completo, por lo que se necesitan más estudios en esta área.

Palabras clave: Antioxidantes; Carcinogénesis; Estrés Oxidativo; Radicales Libres; Revisión.

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INTRODUCTION

A variety of properties, potentially important for human health from fruits and vegetables rich in active compounds denominated phytochemicals happen to be stimulating the importance of the concept of chemoprevention, where the use of natural or synthetic chemical agents act in reverting, blocking or preventing cancer in certain groups of risk[1].

The phytochemicals are product of the secondary metabolism of the plants, selected along the evolution that are stored in their tissues[2]. The antioxidant activity present in some fruits commonly used by the population as "açaí' and "jabuticaba" was already evidenced in the literature, which is being related to the phytochemicals present in the fruits[3,4].

Therefore, these compounds present great potential in preventing diseases for neutralizing the action of free radicals[5]. When these radicals are in great concentrations, they become toxic and interrupt the antioxidant defense system of the organism and can react with different biomolecules, lipids, DNA and proteins, causing them oxidative damages[6]. This oxidative stress can unchain several diseases as diabetes, chronic inflammation, neurodegenerative disorders and many types of cancer[7-9]. One of the manners to help the regulation of this balance is via nuclear factor erythroid-2-related factor 2 (Nrf2) *(*Nrf2*)*[10]. Nrf2 acts in the transactivation of genes with antioxidant response in its promoter region[11]. This way, it can be characterized as a sensor of oxidative stress, responsible for the regulation of the cellular redox balance and protective antioxidant response[12,13]. Complementary to this, Copple[14] emphasizes that factor Nrf2 acts in the expression of more than 200 cytoprotective genes that are related with the neutralization or detoxification of endogenous metabolites and environmental toxins

According to Niture et al.[15], at baseline, Nrf2 is constantly degraded in the cytoplasm by its inhibitor Kelch-Like Epichlorohydrin-Associated Protein 1 (Keap1*)*. For the author, chemical products, including antioxidant present in food, antagonize the interaction Nrf2 and Keap1 and lead to the stabilization and activation of Nrf2[15]. Consequently, the activation and deactivation of this factor of transcription protect the cells against damages of free radicals, prevent apoptosis and promote the survival of the cells[10]. In that manner, it is pursued, through this review, to clarify the quimiopreventive action of phytochemicals through regulation of the Nrf2 transcription factor o.

METHOD

For the present study, it was conducted an integrative review of the literature. The phases of the integrative review were: definition of the theme and design of the study, criteria to select the studies, search and evaluation of the data, interpretation of the results and production of the review. To help in this stage, it were utilized collecting cards containing the year of publication, type of study and principal theme as object of study. The search of the articles was performed in indexed journals in the databases: Academic Google, PubMed, SciELO, ScienceDirect and SpringerLink, utilizing the descriptors obtained from MeSH: phytochemicals, antioxidant, free radicals, phenolic compounds, chemoprevention and Nrf2, corresponding to the language of the database searched; in addition, Boolean operators were used (and/or).

The inclusion criteria to select the studies were: scientific articles including original essays and reviews available electronically, disclosed in Portuguese, English or Spanish in national and international journals from 2000 to 2019. The exclusion criteria were: duplicate articles, dissertations, thesis, abstracts and articles that did not meet the goal of this study.

RESULTS

Through the searches, it was encountered 74 articles that met the inclusion criteria and contained the descriptors selected (Figure 1), however, after reading the abstracts, 16 articles were excluded for not holding direct relation with the study in question or were indexed in more than one database. Therefore, 58 articles remained that were used for the development of the review. Among the publications, 20 articles involved tests *in vivo, in vitro*

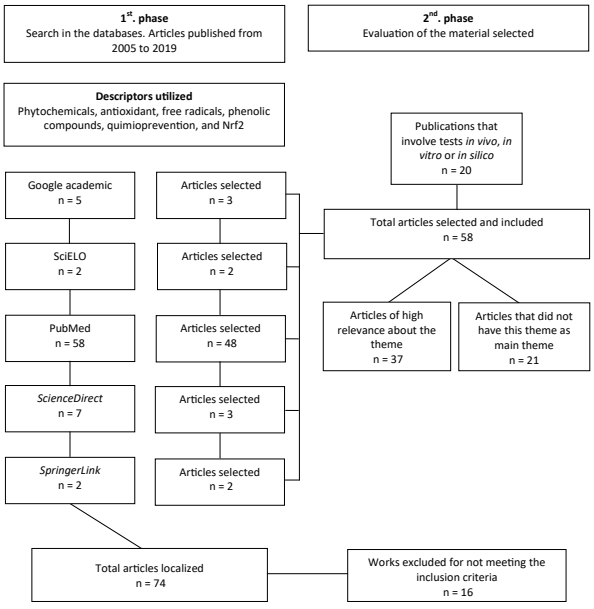

Figure 1. Representative flowchart of the procedures to select the articles

or *in sílico*, nonetheless, only 16 publications involved directly the action of phytochemicals and, consequently, the objectives, compounds involved (when determined from the phytochemicals tests) and conclusions of these articles were presented summarized in Table 1.

DISCUSSION

The carcinogenesis process presents a complex logic, including the generation of great quantity of free radicals[16]. Free radicals are organic and inorganic molecules that have one or more unpaired electrons. Because of this, these molecules become highly unstable and very reactive.

The formation of reactive species can occur in normal conditions in the organism, can be generated in the cytoplasm, in the mitochondria or in the membrane[17]. The Oxygen Reactive Species (ROS) are originated especially when the electrons react with the oxygen during the generation of adenosine triphosphate (ATP), resulting

Table 1. Description of the articles found that performed tests *in vitro* or *in vivo* utilizing phytochemicals

Author/ year	Type of study	Objectives	Compound	Conclusion
Araújo et al., 2013	*In vitro*	Investigate the total antioxidant capacity, the phenolic content and mineral elements of extracts of the fruit and the peel of *Myrciaria cauliflora*	Phenolic compounds	Fruit peel of *M. cauliflora* showed high antioxidant capacity for different methods
Campos et al., 2018	*In vivo*	Test the quimiopreventive effect of "*tucum-do-cerrado*" over the development of colon cancer induced by azoxymethane in mice	There were not performed phytochemical tests to determine the compounds present	"*Tucum-do-cerrado*" reduced the lipid oxidative damage, induced pro-inflammatory effect and promoted a pro-apoptotic "environment" in mice treated with azoxymethane
Chen et al., 2014	*In vitro*	Evaluate if curcumin could inhibit the proliferation of cancer cells of breast cancer through Nrf2 mediated expression of Fen1	Curcumin	Curcumin inhibited the proliferation of cells MCF-7 Fen1-dependent and induced significantly the expression of protein Nrf2 while inhibited the expression of protein Fen1. These data suggest that curcumin can inhibit the proliferation of cells of breast cancer by negative regulation of Nrf2 mediated expression of Fen1, which can be a new mechanism of inhibition of curcumin-induced tumor growth
Cheng et al., 2018	*In vitro*	Reveal the action of resveratrol as activator of Nrf2 and suppressor of the expression of NAF-1 in pancreas cancer cells. Explore the role of NAF-1 as a new molecular target to improve the efficacy of the chemotherapy regimens currently used in patients with pancreas cancer and improve their clinical prognosis	Resveratrol	Resveratrol suppressed the capacity of proliferation and cloning and induced the apoptosis of pancreas cancer cells. These multiple biological effects can result in negative interaction between Nrf2 and NAF-1 in the accumulation of ROS. A production of ROS induced by resveratrol not only leads to the activation of Nrf2, but also inhibits the activity of the transcription of NAF. Therefore, new drugs targets for inhibition of NAF-1 can be a potential therapy to prevent the progression of pancreatic cancer

to be continued

Table 1. continuation

Author/ year	Type of study	Objectives	Compound	Conclusion
Chu et al., 2002	*In vitro*	It was selected 10 common vegetables (broccoli, spinach, yellow onion, red pepper, carrot, cabbage, potato, lettuce, celery and cucumber) based in the US data of per capita consumption and evaluated for the profile of phenolic distributions, including free and bound phenolic, to phenolic antioxidant rate and the antiproliferative activities in cancer cell of human liver HepG2	Phenolic Compounds	Broccoli have more total phenolic content, followed by spinach, yellow onion, red pepper, carrot, cabbage, potato, lettuce, celery and cucumber. Red pepper presented the greatest total antioxidant activity followed by broccoli, carrot, spinach, cabbage, yellow onion, celery, potato, lettuce and cucumber. Spinach showed the greatest inhibitory effect, followed by cabbage, red pepper, onion and broccoli
Eberhardt et al., 2000	*In vitro*	Evaluate the antioxidant and antiproliferative activity of apple extract in the cell lineage of colon and liver cancer	Vitamin C, phenolic acids and flavonoids	Demonstrated that extracts of entire apple inhibit the growth of colon and liver cancer cells. The results indicate that natural antioxidants of fresh fruits can be more effective than a dietary supplement
Hu et al., 2011	*In vitro*	Identify the modifications of the residues of cysteine Keap1 by sulforaphane and investigate if the modification of the residue C151 is essential for the action of sulforaphane	Sulforaphane	The study confirmed that C151 is actually one of the most easily modified cysteines of the Keap1 by sulforaphane
Kode et al., 2008	*In vivo*	Investigate the protective role of resveratrol against oxidative stress caused by the cigarette smoke exposure (CSE) through induction of biosynthesis of glutathione (GSH) via activation of Nrf2	Resveratrol	Resveratrol induces the synthesis of GSH and protects the epithelial cells, reverting the CSE-induced post-translational modifications. These data can have implications in the dietary modulation of antioxidants in the treatment of the chronic pulmonary obstructive disease
Lima et al., 2012	*In vitro*	Characterize chemically and evaluate the bactericide and antioxidant activities of the essential oils of Myristica fragrans and Salvia microphylla	*M. fragrans: Terpin-4-ol, sabineno and* γ*-terpinen S. microphylla: (E) -cariolifeno,* α*-eudesmol,* β*-eudesmol e* γ*-eudesmol*	The essential oils presented bactericide activity. The antioxidant activities of M. fragrans and S. microphylla were demonstrated by the test of b-carotene/linoleic acid, with IC50 976 and IC50 770 lg/ mL for the oils, respectively
Lin et al., 2010	*In vitro*	Evaluate if luteolin has neurotrophic activity, (capacity to induce growth of neurites and attenuate the cytotoxicity induced by the withdrawal of serum in cells PC12)	Luteolin	The discoveries suggest that luteolin induces the growth of neurites and increases the capacity of antioxidant defense, at least in part, by the activation of ERK signaling pathway

to be continued

Table 1. continuation

Author/ year	Type of study	Objectives	Compound	Conclusion
Lippman et al., 2009	*In vivo*	Determine if selenium, vitamins E or both can prevent prostate cancer and other diseases with little or no activity in relatively healthy men	Vitamin E	Selenium or vitamin E, isolated or in combination in doses and formulations utilized did not prevent prostate cancer in this population of relatively healthy men
Marrazzo et al., 2019	*In vitro*	Evaluate the neuroprotective effect of three phytochemicals (sulforaphane, gallate of epigallocatechin and plumbagin), isolated or in combination with focus in its capacity of combatting the oxidative stress	Sulforaphane, gallate of epigallocatechin and plumbagin	In conclusion, it stands out that an appropriate synergic combination of natural antioxidant can help to rescue neuronal cells from cellular death
Salonen et al., 2000	*In vivo*	Study the efficacy of the supplementation of vitamin E and C in the progression of carotid atherosclerosis with the hypothesis of a preventive effect increased in males and smokers and synergism among the vitamins	D-alpha-tocopherol, vitamin C	The supplementation combined in reasonable doses of vitamin E and vitamin C of low release can delay the progression of carotid atherosclerosis common in males. This can imply in benefits in relation to other events based in atherosclerosis
Sun et al., 2002	*In vitro*	Investigate the total phenolic profiles and evaluate the antioxidant and antiproliferative activity in human cells of liver cancer HepG2, of the fruits: apple, red grape, strawberry, pineapple, banana, peach, lemon, orange, pear and grapefruit	Phenolic compounds	Blackberry had the greatest total phenolic content and presented higher total antioxidant activity. Cranberry presented the great inhibitor effect
Xu et al., 2006	*In vitro*	Investigate the roles of the regulated kinases by extracellular signal (ERK) and of c-Jun-NH (2) kinases (JNK) in the regulation of the activity of ARE dependent of isothiocyanate of phenethyl (PEITC) and Nrf2-dependent	Isothiocyanate of phenethyl	The results strongly suggest a model where the treatment with PEITC of cells PC-3 active ERK and JNK, which, on its turn, phosphorylate Nrf2 and induce its translocation to the nucleus. The nuclear Nrf2 activates the ARE and induces the expression of responsive genes to the stress including HO-1
Zuo et al., 2018	*In vitro*	Explore the anticancer potential of luteolin in human colon cancer cells (HCT116 and HT29) and the epigenetic regulation of the pathway Nrf2/ARE	Luteolin	Luteolin suppressed the proliferation and the cellular transformation of the cancer cells. Diminished the methylation of the Nrf2 promoter region, increasing the expression Nrf2

in the formation of the anion superoxide, that can react with other molecules and generate other reactive species as: hydrogen peroxide ($H_2O_2^-$), hydroxyl radical (HR^-) and organic peroxides[18]. The mitochondrial chain also generates nitric oxide that can produce Reactive Nitrogen Species (RNS). In addition, the free radicals can also be acquired exogenously through tobacco-addiction, alcohol use, exposure to radiations among other[19,20].

According to Oliveira et al.[21], when present in low concentrations, free radicals show benefic effects in the cellular response and in the immune function. The imbalance between free radicals and antioxidants results in the induction of cellular damages, called oxidative stress[22]. The oxidative stress induced many pathological alterations, including inflammation and cancer. It is believed that chronic inflammation is strongly associated to the main stages of carcinogenesis[23].

The three stages of carcinogenesis include initiation, promotion and progression. In its basic form, this process involves the genetic modification of genomic DNA; that is, with the formation of a mutated cell, it ensues its selective growth. This growth can be stimulated by an increase in the rate of cellular division and/or by a reduction of the rate of death (apoptosis) of the mutated cell. While the mutated cell divides itself, the genetic alterations occur in the recent formed lesion. Briefly, these three stages involve different biological events as: DNA mutation, cellular proliferation and metastasis[24.25]. In this sense, nutrigenomic, as a science that analyzes the interactions between nutrients and bioactive compounds of food, presents like a promising area for studies of the effects of bioactive compounds in carcinogenesis[26]. It is evident, here, that the oxidative damages can be prevented or minimized by the antioxidant encountered in the fruits and vegetables[27]. Recent studies showed also that some dietary phytochemicals antioxidants (as natural tocopherol, carotenoids and flavonoids) are important defensive factors that protect against the oxidative stress[28]. In this way, incorporate vegetables in the diet with its phytochemical properties is essential for the modulation of the oxidative stress and its possible effects.

Among the diversified mechanisms of action of the phytochemicals, for modulation of the oxidative stress, is encountered the potential of oxidoreduction of certain molecules, that is, the capacity that these molecules have to compete for active and receptive sites in the several cellular structures, like the modulation of the expression of genes that codify the proteins involved in intracellular mechanisms of defense[29].

According to Li et al.[23], there are many phytochemicals with quimiopreventive properties of cancer, exerting antioxidant and anti-inflammatory functions through the activation of the pathway Nrf2. The Nrf2 transcription factor belongs to the family cap'n'collar of basic factors of transcription of region-leucine and performs a crucial role in the regulation of the oxidative stress and of the inflammation, manipulating the main genes of the antioxidant enzyme and of detoxification through the antioxidant response element (ARE)[30]. Under baseline conditions,, the Keap1 or INrf2 regulates the activity of Nrf2, keeping the dynamic balance of cytoplasmatic Nrf2 for functioning as an intermediate for the binding of the Nrf2 with the complex E3-ubiquitin ligase complex/Ring box protein 1 (Cul3-Rbx1), which is the responsible for the ubiquitination of this factor for its posterior proteasomal degradation[31]. In that manner, the binding of Keap1 to Nrf2 represses the transcription of the genes mediated by Nrf2, under homeostatic conditions. After the exposure to oxidative stress or positive stress by phytochemicals can occur the release of Nrf2, of the repression done by Keap1, achieving, therefore, the trans locus to the core, where the proteins small musculoaponeurotic fibrosarcoma (sMaf) associate. This heterodimer binds to ARE or to the electrophilic response element (EpRE), located in the promoter region of target-genes. In that manner, occurs the induction of the production of antioxidants[15].

Further to the maintenance of the redox balance and of the xenobiotic metabolism by the induction of expression of antioxidant and detoxifying enzymes, Nrf2 can also regulate numerous genes involved in the cellular differentiation, proliferation, apoptosis, among others[32,33]. It can as well, modulate and influence diverse cellular activities as inflammation, tissue regeneration and metabolic reprograming because of functional interactions with different pathways of signalization[34]. The quimioprevention, done by the phytochemical, through activation of the factor of transcription Nrf2, was observed in several studies. Zuo et al.[16] explored the luteolin anticarcinogenic potential, a common flavonoid originated from vegetables, fruits and herbs in cancer cells of the human colon and the epigenetic regulation of the pathway Nrf2/ARE. The results of the study showed that luteolin suppressed the cellular proliferation and the cellular transformation of the cells HCT116 (human colorectal carcinoma) andHT29 (adenocarcinoma of the human colon) in dose-dependent manner. The genomic sequencing of the bisulfite revealed that the methylation of the Nrtf2 promoter region was reduced by luteolin with the expression increased of RNAm of Nrf2. Diminished levels of protein and enzymatic activity of epigenetic modifying enzymes such as methyltransferases DNA (DNMT) and histones deacetylases (HDAC), were also observed in cells HCT116 treated with luteolin. The authors suggest that luteolin can exert its antitumoral activity in part through epigenetic modifications of the gene Nrf2, with subsequent induction of its pathway of antioxidant stress downstream.

Studies that analyze the role of phytochemicals in the Nrf2 transcription factor in liver cancer cells were also conducted. Ren et al.[35], utilizing sulforaphane of benzyl (BSFN), derived from sulforaphane (SFN), a isothiocyanate encountered in cruciferous vegetables for

the prevention of cancer in cells of the human hepatoma (HepG2), verified that the sulforaphane of benzyl can induce the cellular apoptosis by dependent pathway of mitochondria, which inhibits the growth of cells HepG2 in a dependent mode of time and concentration. In addition, NSFN could inhibit the AKT/MAPK, that are important pathways in the development of cancer and activate the Nrf2 pathway/ARE in cells HepG2.

Some phytochemicals as resveratrol, the curcumin and isothiocyanate are natural compounds quite studied in relation to its quimiopreventive properties. A recent study conducted by Cheng et al.[36], demonstrates that resveratrol, found in grapes, in peanuts among other varieties of fruits and food products as red wine suppresses the expression of the factor of autophagia of privation of nutrients -1 (NAF-1) in pancreatic cancer cells, inducing the accumulation of ROS and activating the signaling of Nrf2. In addition, the suppression of NAF-1 activates the apoptosis and blocks the proliferation of pancreatic cancer cells. In the study of Chen et al.[37], it was observed that curcumin, a polyphenol encountered in saffron can inhibit the proliferation of breast cancer cells through negative regulation of the expression of endonucleases Flap 1 (Fen1), a specific nuclease of repair of DNA mediated by Nrf2. In this study, the authors demonstrated that curcumin inhibited the proliferation of cells MCF-7 (cell lineage of adenocarcinoma of human breast) Fen1-dependent and significantly induced the expression of the protein Nrf2, while inhibited the expression of protein Fen1.

The isothiocyanate studied in the review of Houghton et al.[38], encountered in broccoli, has shown to be a high potency inducer in the activation of Nrf2. In addition, it performs an important role in relation to the mechanisms of biological activities, including the selective cytotoxicity in carcinogenic cells, having the capacity of destroying specific cells through the liberation of this substance as well as the regulation of defense mechanisms that protect the cells against the oxidative stress[39].

In the study of Ramos-Gomes et al.[40], it was demonstrated that Nrf2 deficient mice did not respond to the protection of antioxidant, being more susceptible to unchain a carcinogenic process. This way, phytochemicals as isothiocyanate present in broccoli, resveratrol present in grapes and curcumin present in saffron are powerful inducers of Nrf2 and of the enzymes of detoxification, increasing the antioxidant capacity of the cell.

Therefore, it is possible to observe that many photochemicals of the diet have powerful capacities in the regulation of the system Nrf2/Keap1. However, the molecular mechanisms involved in this area are not well classified. In a study of review performed by Qin e Hou[41], the molecular mechanisms of the Nrf2 regulation by phytochemicals of the diet were revised and the authors classified them in Keap1 dependent and Keap1 independent.

In the Keap1 dependent pathway, can occur modifications of cysteine, ubiquitination, phosphorylation and succination of Keap1[41]. An enormous number of photochemicals in the diet was found for modifying the cysteine of Keap1 and regulate the Nrf2/Keap1 system. Among them, the sulforaphane[42] and resveratrol[43]. In the Keap1 independent mechanism, can occur phosphorylation of the kinases-proteins (PKC, PI3K, MAPKs, GSK3 and PERK), and some factors of transcription can bind to ARE in order to positively or negatively regulate the expression of genes regulated by Nrf2. In addition, the epigenetic modifications can also establish a mechanism as the methylation of DNA of promoters, modifications of histones, acetylation or methylation and adjustment of microRNA by transcriptional regulation[41].

Studies already demonstrate that the phosphorylation of kinases (ERK) can be promoted by sulforaphane[44], resveratrol[45] and luteolin[30]. The activity of PI3K kinases protein can be stimulated by sulforaphane[46] and resveratrol[45]. Some phytochemicals of diet are considered potent epigenetic modifiers, including isothiocyanates and curcumin[47]. In Figure 2, it can be observed the activation of the Nrf2 transcription factor dependent and independent from Keap1.

There are numerous natural compounds capable of inducing detoxifying enzymes through the Nrfs signalization pathway that are reported as potential cancer quimiopreventive agents[48,49]. Therefore, the phytochemicals inducers of the Nrf2 transcription pathway exert favorable quimiopreventive effects through different antioxidant mechanisms and can contribute for the reduction of the formation of tumors, after the reduction of the levels of ROS. These actions protect the cell against oxidative and inflammatory damages that can unchain a possible carcinogenic process[50].

However, for Tebay et al.[51], the activation by Nrf2 can induce the activity of some genes that contribute for the chemical carcinogenesis, promoting the futile redox cycle of metabolites of polycyclic aromatic hydrocarbons just as they can offer resistance to chemotherapy drugs, increasing the expression of efflux pumps. For this, it is suggested that its cytoprotective effects can vary according to the specific modeling of the context. Regardless the recent discoveries of the Nrf2 oncogenic role in cancer cells, the therapeutic use must be conducted cautiously, being necessary more studies to confirm the beneficial and safe use as quimiopreventive agent without the risk of developing severe side effects[52].

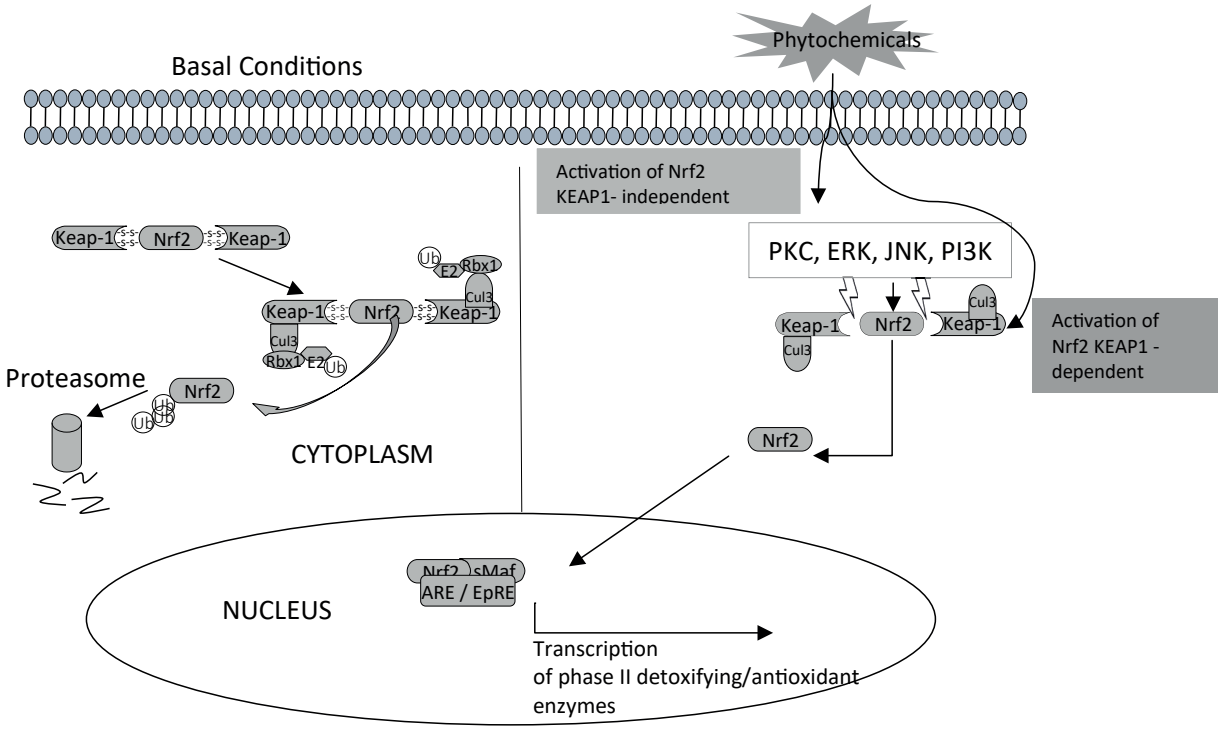

Figure 2. Signaling pathway of nuclear factor-erythroid-2–related factor 2 (Nrf2) Keap1 dependent. In the cytoplasm Nrf2 is repressed by the protein associated to the Kelch-like ECH cytoskeleton associated to protein 1 (Keap1). Keap1 has a domain to associate to specific-substrate adaptors proteins related to the ligase ubiquitin (Cul3, Rbx, E2). PKC: C protein kinase; ERK: Protein kinase regulated by extracellular signal; JNK: c-Jun N-terminal kinase; PI3K: Phosphotidilinositol-3-kinase; Ub: ubiquitination; Cul3: Ubiquitin ligase; Rbx: Adaptor protein 1; E2: ubiquitin conjugating enzyme; sMaf: Small musculoaponeurotic fibrosarcoma; ARE: antioxidant response element; EpRE: element of electrophilic response.

Source: The author.

It is important to emphasize that the treatments reported previously were in cells *vitro* or *in vivo* with laboratory animals in controlled conditions and in specific concentrations and presented favorable biological effects. In this sense, it is possible to preview that a proper combination of said phytochemicals compounds has greater and better therapeutic effect. Still, the hypothesis is that the dose and the ideal time of treatment with phytochemicals for humans will depend of various gradients of concentration of endogenous effectors molecules[53], in addition to pre-disposed genetic factors.

For Salonen et al.[54], the dietary use of isolated phytochemicals does not reproduce the same results when compared to the effects of the use of whole compounds. The justification more accepted in the scientific environment for the fact of this difference of bioactivity and/or bioavailability would be in the addictive and synergic actions of the innumerous elements present in the vegetal tissues that form food and/or vegetal extracts[55]. In that sense, the synergy of the phytochemicals elements present in food and/or vegetal extracts and not the action of an isolated compound would be responsible for bioactivity[56-58].

However, the studies presented in this review evidence the repercussion in the scientific mean in relation to the importance of phytochemicals present in the human food diet, in helping the activation of this pathway that plays an essential role in the antioxidant response and balance of the oxidative stress[11].

CONCLUSION

Based in the arguments, the conclusion is that the phytochemicals participate actively of the Nrf2 transcription pathway and exert quimiopreventive effects through the antioxidant mechanisms and can contribute for the reduction of the formation of tumors.

It is observed still that Nrf2 transcription factor, after the loss of the redox balance, is naturally activated as an endogenous compensatory mechanism. However, several phytochemicals of the diet, such as resveratrol, isothiocyanate, luteolin among other can help in the activation of this pathway. In that manner, understand the core issue of action, present in the phytochemicals can contribute for the improvement of new tactics that permit to help in the development of the functioning of

the organism. However, further studies are necessary to identify all the subjacent mechanisms to the activation of Nrf2, analyzing the phytochemicals present in the diet in order to be possible to establish its protective effects with more safety.

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DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

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