Perspectives of The Use of Sulforaphane In Animal Model of Colorectal Carcinogenesis in Brazil: A Review

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Abstract

Colon cancer is a growing health problem in Brazil. According to data from the World Health Organization (WHO), colon cancer is among the top ten causes of mortality and morbidity in the world. Besides, the disease has a significant economic impact on the Brazilian public health system. Over the past five years, there has been an increased interest in use, isolation, characterization and determination of the biological actions of compounds such as broccoli. Experimental studies with genetically modified (GMOs) rats, mice, and rats using Sulforaphane have demonstrated their ability to prevent, delay and reverse pre-neoplastic lesions, improved survival, as well as acting on neoplastic cells with therapeutic action. Sulforaphane through activation of Nrf2 increases the activity of phase II enzymes such as glutathione S transferase

(GST), which is involved in the elimination of xenobiotic compounds. Aberrant crypts are induced, in Wistar rats and mice, by genotoxic and non-genotoxic chemical compounds. Colon carcinogenesis is generally induced in rats and mice by two substances, 1,2-dimethylhydrazine (DMH) and azoxymethane (AOM). Azoxymethane is often used concerning DMH because it is more potent and requires few reactions for its activation. It is possible to conclude that Sulforaphane, through its various biological actions, presents efficiency in the prevention of colon cancer and significant potential for use in future experimental studies with genetically modified rats, mice, and rats.

Keyword: Sulforaphane, Colonic Neoplasms, Rats, Azoxymethane, Broccoli

1. Introduction

Colon cancer is a growing health problem in Brazil[01,02]. It is related to the aging of the population[01,02,03,04,05], with the incidence of risk factors[01,04], such as little practice of physical activity associated with overweight, smoking, alcohol use and excessive consumption of fat and red meat[01,03]. Still, it can be defined as genetic alterations that occur with the loss of control of the mechanisms of cell division, and thus[06] allow disordered multiplication of cells[07]. Colorectal cancer prevention studies show that the primary pathway unregulated signaling in different types of cancer has been affected by inadequate nutrient intake[08-11].

The difficulty in effectively diagnosing the disease, especially the identification of primary stages of tumors[04,10], as well as the few treatments available for patients with advanced staging and the resistance of tumors to multiple drugs, has contributed to the increase in cases of the disease.[06-28,] and thus reinforces the need to expand efforts to prevent cancer[01,04].

2. Epidemiological aspects of colorectal cancer

According to data from the World Health Organization (WHO), colon cancer is among the top ten causes of mortality and morbidity in the world[12,13].

In 2018, there were 36,360 cases of colon cancer in Brazil[01], so there is an estimate that over the next two decades the number of new cases of colon cancer in the world will gradually increase in geometric progression[14] and may cause about 13.2 million deaths annually[02,12,13]. The highest incidence of tumors in the colon occurs in low and middle-income countries[02,15], as is the case in Brazil[01,02]. The incidence rate of new colon cancer cases published by the National Cancer Institute[01,02] was around 324.58 cases per 100,000 inhabitants for men and 310.30 for women[01].

Besides, the disease has a significant economic impact on the Brazilian public health system[01,02], and in the years 2017 to 2018, the total cost of colon cancer was estimated at approximately $ 1.14 billion (USD) in the Unique Health System (SUS)[01].

3. The anticarcinogenic effect of sulforaphane

Over the past five years[05], increased interest in use[08,12], isolation[08], characterization[03] and determination of the biological actions of compounds such as broccoli[03] have demonstrated efficiency by the increasing number of publications[01-32], and all studies carried out intending to analyze Sulforaphane, specifically its anticarcinogenic activity[18,23,33].

In the last ten years, has been identified more than 1000 different types of phytochemicals[14] with protective activities against cancer[29,34]. Broccoli, a plant of the cruciferous family[25,27], in the feeding process[27], specifically at the time of chewing, releases an enzyme called myrosinase[25,26,27], which degrades the glucoraphanin present in this vegetable[25]. Turning it into Sulforaphane[9], which is considered the bioactive compound[09,25], capable of activating the transcription factor NRF2, which is an essential anticarcinogenic signaling molecule[6].

Therefore, for years, experimental studies with genetically modified (GMOs) rats, mice, and rats using Sulforaphane have demonstrated their ability to prevent, delay and reverse pre-neoplastic lesions[17,21,22], improved survival[16,22], as well as acting on neoplastic cells with therapeutic action[20,22]. For example, some experimental, epidemiological studies of genetically modified rats, mice, and rats over the past five years have provided strong evidence of protection against some cancers through the consumption of cruciferous vegetables rich in sulforaphane[15,14,23] like of the broccoli[9,21].

4. Colorretal carcinogenesis in animal models

Animal models with rats[06], mice and genetically modified rats (GMOs) are classically used for in vivo experimental chemical carcinogenesis and require extended follow-up of animals to observe the development of intestinal neoplasia[6,32]. Therefore, developing affinity biomarkers for incipient colon tumors[10,25] may show premalignant structural alterations of the colonic mucosa[07-10,25], called aberrant crypts[07,9]. Over the past ten years, aberrant crypt foci have been accepted as pre-neoplastic lesions of colon carcinogenesis because they can be characterized by histopathology[07,09], biochemical alterations associated with genetic mutations and epigenetic events[07,27]. Aberrant crypts are induced, in Wistar rats and mice, by genotoxic and non-genotoxic chemical compounds[07-10,17]. Colon carcinogenesis is generally induced in rats and mice by two substances[6], 1,2-dimethylhydrazine (DMH) and azoxymethane (AOM)[10,14,31]. The DMH is characterized as an indirect inducing chemical with the ability to promote DNA hypermethylation of colorectal epithelial cells[10,29]. AOM differs from DMH[14,18,29] because it is characterized by being a direct inducer without relying on in vivo conversion[11,18]. Generally, AOM-induced lesions[11,14] are K-ras[7], APC, and p53 mutations[27], similar to what occurs in RCCs in humans and can be found in other organs[07,27] such as liver, small intestine, and peritoneum[10]. AOM is known as a DMH metabolite[14,32], with a mechanism of induction of preneoplastic lesions which confers increased expression of the c-fos gene followed by a decrease in the c-Myc gene[32] as it occurs with the mutation of the K-ras gene, which are similar transformations to those observed in spontaneous carcinogenesis in humans[10,33].

Azoxymethane is often used concerning DMH because it is more potent and requires few reactions for its activation[14,27]. This metabolite is activated in the liver by N-oxidation. It generates reactive compounds essential for chemical carcinogenesis to occur[07,10,14,] and so to be carried into the bloodstream or bile duct

with conjugated glucuronide[14,30]. After the activation process, DNA is methylated mainly at the N7-guanine and 06-guanine position[06,25,30].

5. Sulforaphane action molecular mechanism

It is noteworthy that Sulforaphane interacts with several molecular targets[14]; however, it is possible to evaluate that through the Nrf2 pathway, its mechanism of action is much better described[10,20]. Sulforaphane is known as a central transcription factor in the regulation of cellular redox state[21,22], so the cell receives stimulation that will not suppress Keap1 proteins[20,22] and thus does not cause ubiquitination with further degradation of Nrf2[20-22]. Sulforaphane can interact with the Keap1 protein[21,24], hindering Nrf2-Keap1 interaction and subsequently can break this chain[02,14,20-23,31], thus allowing Nrf2 activation and nuclear translocation[20-22]. In the cell, nucleus Nrf2 binds to the antioxidant response element known as ARE[22,23], which is a region of DNA that promotes genes encoding antioxidant enzymes including[11,20-22], for example, NAD (P) -H-quinone oxidoreductase-1 (NQQ1), heme oxygenase-1 (HO-1)[11,22].

It is possible to observe through evidence from studies published in the last six years that the induction of phase II enzymes should be one of the factors by which cruciferous vegetables confer practical health benefits[05,33]. Because Sulforaphane, through activation of Nrf2, increases the activity of phase II enzymes such as glutathione S transferase (GST)[14,20-22,32], which is involved in the elimination of xenobiotic compounds[22,33].

6. Conclusion

Thus, it is possible to conclude that Sulforaphane, through its various biological actions, presents efficiency in the prevention of colon cancer and significant potential for use in future experimental studies with genetically modified rats, mice, and rats in Brazil. Besides, there should be explored further studies with adverse effects on the ingestion of high doses of these compounds, consumption of fortified products, capsule supplements, or alternative forms of pharmaceutical presentation such as raw vegetables.

7. References

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