Substâncias anticâncer na dieta humana

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1. Cancer in the world
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6. Cancer in the world
The International Agency for Research on Cancer (IARC) estimated that 14.1 million new cancers were diagnosed and that 8.2 million patients died of the disease worldwide in 2012 alone.

GLOBOCAN data 2012

According to the National Cancer Institute (NCI), healthcare costs associated with the diagnosis and treatment of cancer in the Uniteated States currently exceed $ 125 billion per year and projected to be $ 173 billion in 2020.

Mariotto et al. 2011, Journal of the National Cancer Institute
CANCER IN THE WORLD

GLOBOCAN data 2016
CANCER IN BRAZIL

437,592 new cases in 2016

733,340 predicted new cases in 2030

393,545 predicted number of cancer deaths in 2030

GLOBOCAN data 2016
CHEMOPREVENTION

The pharmacological intervention with synthetic or naturally occurring compounds that may prevent, or reverse carcinogenesis, or prevent the development of invasive cancer.

Dietary consumptions of foods is a convenient method of administering potentially chemopreventive phytochemicals in a cost-effective manner.

Gullet et al. 2010, *Seminars in Oncology*, 37, 258-281
Source of Natural Cancer Preventive Compounds

Curcumin

Resveratrol

Genistein

Curcuma Longa

Vitis vinifera

Glycine max
Source of Natural Cancer Preventive Compounds

Glucosinolates

Brassicaceae (Cruciferae)

Hesperidin

Citrus
Source of Natural Cancer Preventive Compounds

Gingerols

Ginsenosides

Zingiber officinale

Panax ginseng
Source of Natural Cancer Preventive Compounds

Capsaicin

*Capsicum L.*

Lycopene

*Solanum lycopersicum*

Alliin

Allicin

*Allium sativum*
Source of Natural Cancer Preventive Compounds

(-)-epigallocatechin-3-gallate (EGCG)

Camellia sinensis

Punicalagin

Punica granatum L.
AN OVERVIEW OF CARCINOGENESIS PROCESS

Kotecha et al. Oncotarget, 2016
AN OVERVIEW OF CARCINOGENESIS PROCESS

Warburg effect

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Effect of Curcumin on breast cancer cell lines (MCF7/MDAMB-231)
Effect of Resveratrol on breast cancer cell lines (MCF7/MDAMB-231)

Brasili E, Cechinel VF. *Crit Rev Food Sci Nutr.* 2015
NUTRI-EPIGENETICS

EPIGENOME is affected by dietary phytochemicals

DNA methylation is inhibited by phytochemicals during carcinogenesis

Clarissa Gerhauser, Top Curr Chem, 2012
Dietary phytochemicals impart anticancer properties by Histone Modifications

- **Activity:** Butyrate*, SFN*, PEITC, PHI, EGCG, DADS, Allylmercapatan, Apicidin, A-Keto-γ-methylselenobutyrate
- **Expression:** DIM*, Genistein, Parthenolide

**“Open” chromatin**
- HDACs
- Sirtuins
- Anacardic acid, Garcinol, Curcumin, Gallic acid, EGCG, Delphinidin, Genistein (expr)

**“Closed” chromatin**
- HMTs
- HDMs
- Activity: Chaetocin, EGCG, Curcumin, Genistein, n-3 PUFA
- Polyamine analogues

*Clarissa Gerhauser, Top Curr Chem, 2012*
microRNAs regulation by dietary phytochemicals

EGCG Resveratrol Curcumin

Liver cancer

miR-16 miR-21

miR-16 Bcl-2 AR

miR-25 miR-103

miR-141 miR-663

miR-17 miR-21 miR-25 miR-103

miR-203

Transcription factors

RNA Pol II/III

Comet cancer

miR-15a

Apoptosis

Curcumin Genistein Daidzein

Breast cancer

Resveratrol

miRNA processing

Ago2

Dicer

Nucleus

Epigenetic alterations

5’ 3’

Target degradation

5’ 3’

Translational repression

Molecular Mechanism Underlying the Antitumor Effects of Curcumin in Pancreatic Cancer Cell Growth

Bimonte et al. *Nutrients*, 2016, 8, 433
GUT METABOTYPES GOVERN HEALTH EFFECTS OF DIETARY PHYTOCHEMICALS

- **Duodenum**
  - $10^1-10^3$ cfu/ml
  - Lactobacillus
  - Streptococcus

- **Distal Ileum**
  - $10^7-10^8$ cfu/ml
  - Clostridium
  - Bacteroides sp
  - Coliforms

- **Colon**
  - $10^{11}-10^{12}$ cfu/ml
  - Clostridium coccoides
  - Clostridium leptum
  - Fusobacterium
  - Bacteroides
  - Bifidobacterium

- **Stomach**
  - $10^1-10^3$ cfu/ml
  - Lactobacillus
  - Candida
  - Streptococcus
  - Helicobacter pylori
  - Peptostreptococcus

- **Jejunum**
  - $10^2$ cfu/ml
  - Lactobacillus
  - Streptococcus

- **Proximal Ileum**
  - $10^3$ cfu/ml
  - Lactobacillus
  - Streptococcus
  - Actinobacteria
Microbiota as a mediator of cancer progression and therapy

Butyric acid acts as a potent antineoplastic agent:
- inhibits growth and induces differentiation
- interferes with the pathogenesis of colorectal cancer
- arrests growth of neoplastic colonocytes in G1
- modifies genic expression of genes involved in chemotherapy resistance and in cell proliferation/differentiation
- induces apoptosis by a p53-independent pathway
BUTYRATE PARADOX

In spite of its early promise, butyrate is not among the drugs used for cancer treatment.

The major problem is achieving and maintaining its millimolar concentrations in blood.

Dallas R. Donohoe et al. Oncotarget 2013, 4: 182-183
Butyric acid

TRIBUTYRIN: a Stable and Rapidly Absorbed Prodrug of Butyric Acid

It is a triacylglycerol composed of three butyric acid molecules esterified with glycerol

It is a prodrug of natural butyrate: 1 molecule of tributyrin may generate 3 molecules of butyric acid

It is rapidly absorbed and is chemically stable in plasma: it diffuses through biological membranes and is metabolized by intracellular lipases, releasing therapeutically effective butyrate over time directly into the cell.

Compared with butyrate, tributyrin has more favorable pharmacokinetics and is well tolerated.
Tributyrin has potent antiproliferative, proapoptotic and differentiation-inducing effects in neoplastic cells.

Heidor et al., *Current Drug Targets*, 2012, 13, 1720-1729
Suppressing activity of tributyrin on hepatocarcinogenesis is associated with inhibiting the p53-CRM1 interaction and changing the cellular compartmentalization of p53 protein

Juliana F. Ortega\textsuperscript{1}, Aline de Conti\textsuperscript{2}, Volodymyr Tryndyak\textsuperscript{2}, Kelly S. Furtado\textsuperscript{1}, Renato Heidor\textsuperscript{1}, Maria Aderuza Horst\textsuperscript{1}, Laura Helena Gasparini Fernandes\textsuperscript{1}, Paulo Eduardo Latorre Martins Tavares\textsuperscript{1}, Marta Pogribna\textsuperscript{2}, Svitlana Shpyleva\textsuperscript{2}, Frederick A. Beland\textsuperscript{2}, Igor P. Pogribny\textsuperscript{2}, Fernando Salvador Moreno\textsuperscript{1}

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Male Wistar rats

- Human HCC PLC/PRF/5 (p53 mutant)
- Rat HCC JM1 cell line

Tributyrin (200 mg/kg)

Formation of preneoplastic lesions

Sodium butyrate (0-10 mM)

Cell Proliferation and Apoptosis

Expression and Localization of p53 protein and CRM1 protein
Effect of tributyrin on the formation of preneoplastic lesions

Table 1: Morphometric analysis of GST-P positive foci in the livers of rats subjected to a “resistant hepatocyte” model of hepatocarcinogenesis (control group) and treated with tributyrin during the promotion phase

<table>
<thead>
<tr>
<th>Groups (n)</th>
<th>Number of GST-P positive PNL per cm²</th>
<th>Size of GST-P positive PNL (mm²)</th>
<th>Area of liver section occupied by GST-P positive PNL (%)</th>
<th>BrdU positive hepatocytes/mm² PNL</th>
<th>Hepatic apoptotic bodies/mm² PNL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (6)</td>
<td>61 ± 4</td>
<td>0.38 ± 0.09</td>
<td>25 ± 2</td>
<td>12.11 ± 5.85</td>
<td>0.37 ± 0.34</td>
</tr>
<tr>
<td>Tributyrin (8)</td>
<td>55 ± 4</td>
<td>0.19 ± 0.01*</td>
<td>10 ± 1*</td>
<td>6.68 ± 6.61</td>
<td>2.23 ± 0.89*</td>
</tr>
</tbody>
</table>

Effect of tributyrin on the extent of cell proliferation and apoptosis

Ortega J et al. 2016 Oncotarget
Effect of tributyrin and sodium butyrate on the level and localization of p53 protein

Ortega J et al. 2016 Oncotarget
Effect of tributyrin and sodium butyrate on the level and localization of CRM1 protein

Ortega J et al. 2016 Oncotarget
interaction of p53 with CRM1 protein

Ortega J et al. 2016 Oncotarget
The treatment with tributyrin during the promotion stage of liver carcinogenesis:

- greatly reduced the number, size, and area of the GST-P positive preneoplastic foci
- increased the activation of apoptotic cell death in GST-P-positive lesions
- increased the nuclear level of p53 protein *in vivo* and *in vitro*
- reduced the binding interaction between CRM1 and p53

**Tributyrin** and **Sodium butyrate** exhibit a potent ability to prevent and/or inhibit carcinogenesis, including hepatocarcinogenesis.
CONCLUSIONS

Discrepancies between dietary bioactive compounds putative effects may in part be explained by differences in **intake levels** and their **bioavailability**.

Dietary bioactive compounds may not act efficiently in isolation but together with many other compounds in the food matrix, leading to **synergistic effects**.

The influence of consuming a mixed diet, i.e. “real” complex meals, on bioaccessibility and absorption is poorly comprehended, and further studies to investigate the effect of different dietary bioactive compounds during carcinogenesis process should be performed.