



Targeting Colorectal Cancer with Dietary Bioactive Agents

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Outline

A) Hyperhomocysteinemia

B) Dietary bioactive agents

C) Colorectal cancer

A) Hyperhomocysteinemia

- Hyperhomocysteinemia (Fasting serum homocysteine $>15 \mu\text{mol/L}$)
- Hyperhomocysteinemia has been divided into:
 - ✓ Mild (15 – 29.99 $\mu\text{mol/L}$)
 - ✓ Intermediate (30 – 99.99 $\mu\text{mol/L}$)
 - ✓ Severe ($\geq 100 \mu\text{mol/L}$)

Modifiable Causes of Hyperhomocysteinemia

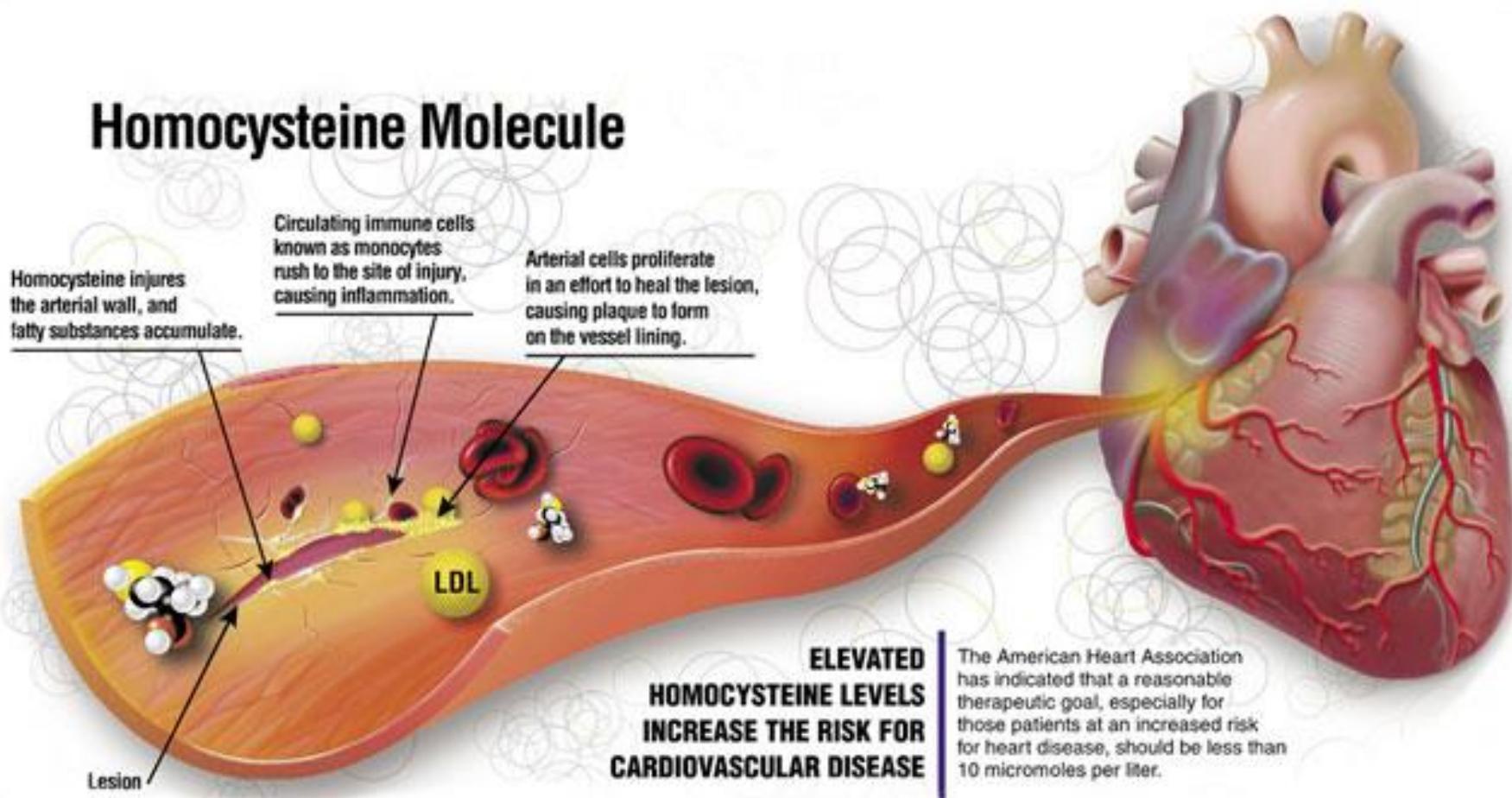
- Low nourishments of specific nutrients (Folate, vitamins B6 and B12)
- Smoking
- Coffee drinking
- Fatty liver and alcohol consumption
- Obesity

Non-modifiable Causes of Hyperhomocysteinemia

- Inborn errors of metabolism
- Severe renal failure
- Vitamin B12 antagonists
- Antileptic drugs
- Hypothyroidism
- Hyperproliferative disorders
- Thermolabile MTHFR (Methylene Tetrahydrofolate Reductase).

Physical Consequences of Hyperhomocysteinemia

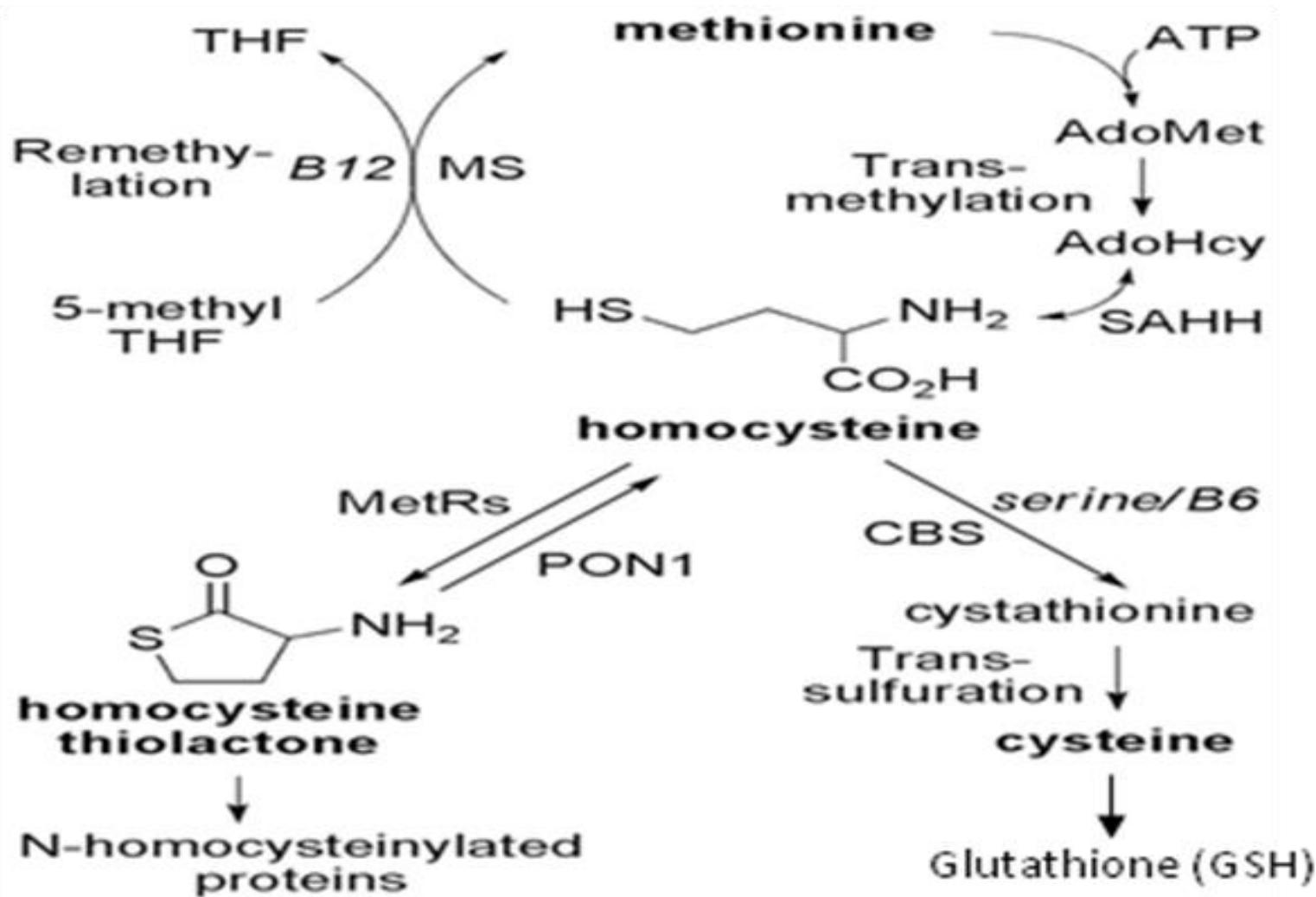
Homocysteine Molecule

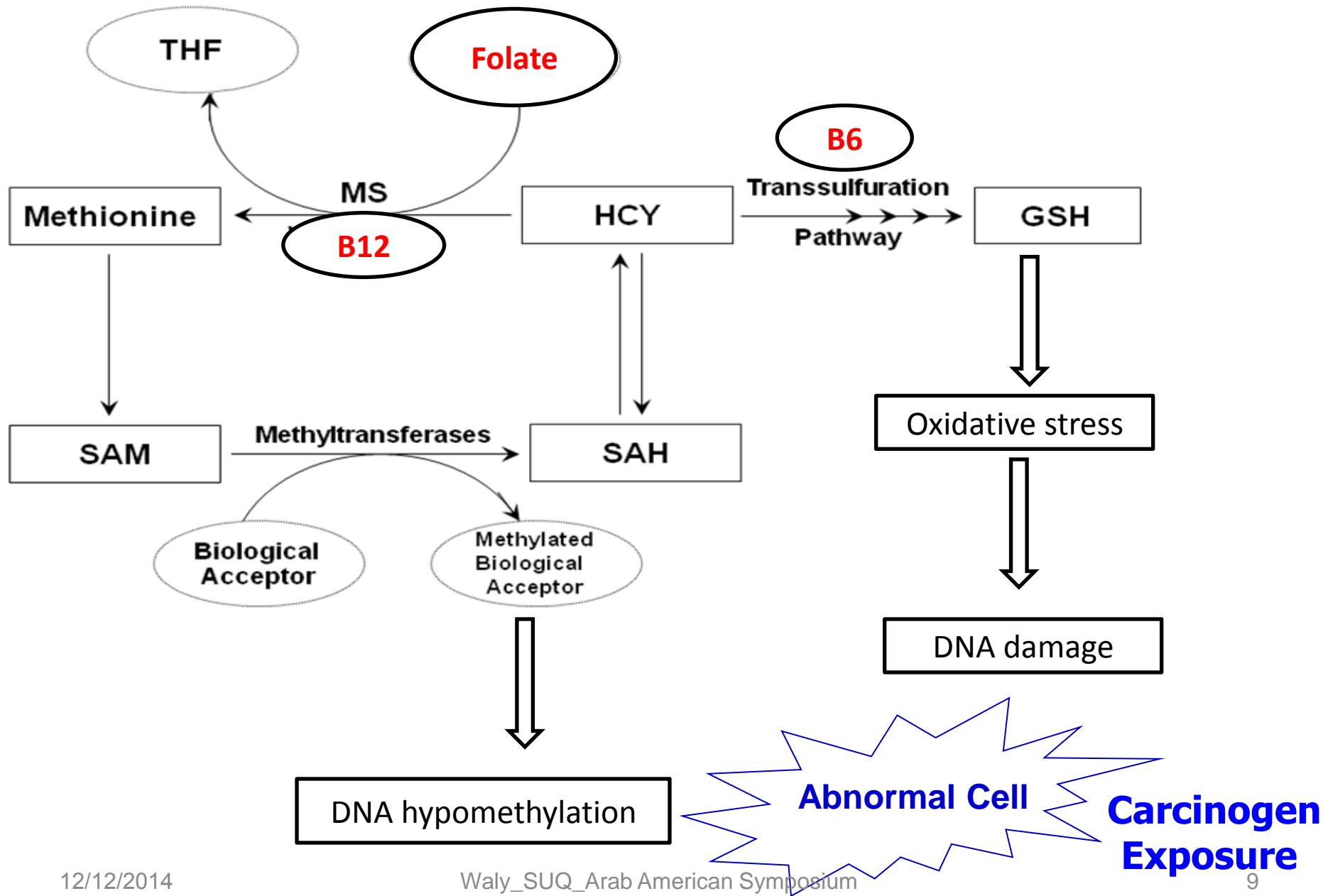


The American Heart Association has indicated that a reasonable therapeutic goal, especially for those patients at an increased risk for heart disease, should be less than 10 micromoles per liter.

Metabolic Consequences of Hyperhomocysteinemia

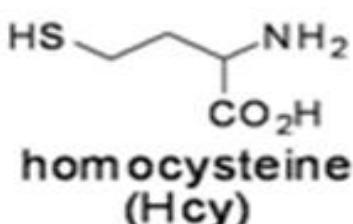
- Oxidative stress
- DNA hypomethylation
- Formation of N-homocysteinylated proteins



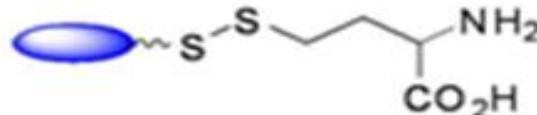


A.

protein thiol



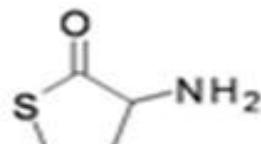
S-Homo-Cysteinylolation
Reversible



Disulfide Linkage

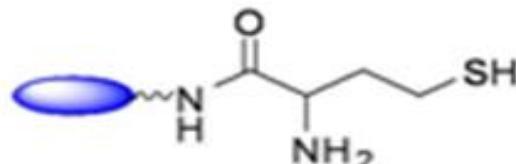
B.

protein amine

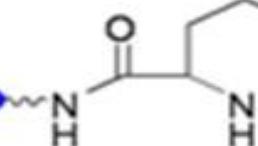
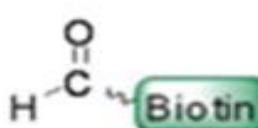


homocysteine thiolactone (Hcy TL)

N-Homo-Cysteinylolation
Irreversible



Amide Linkage



Biotin-labeled protein via a 1,3-thiazine linker

Control Sample

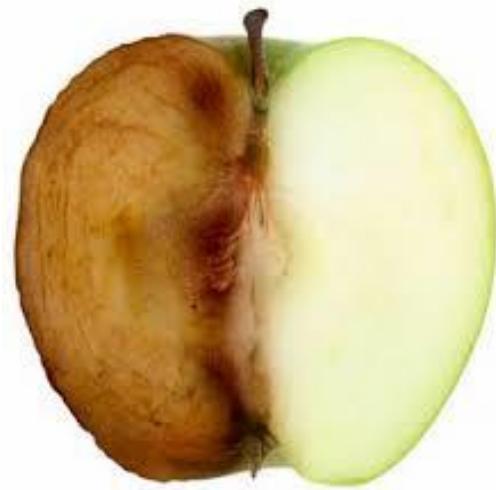
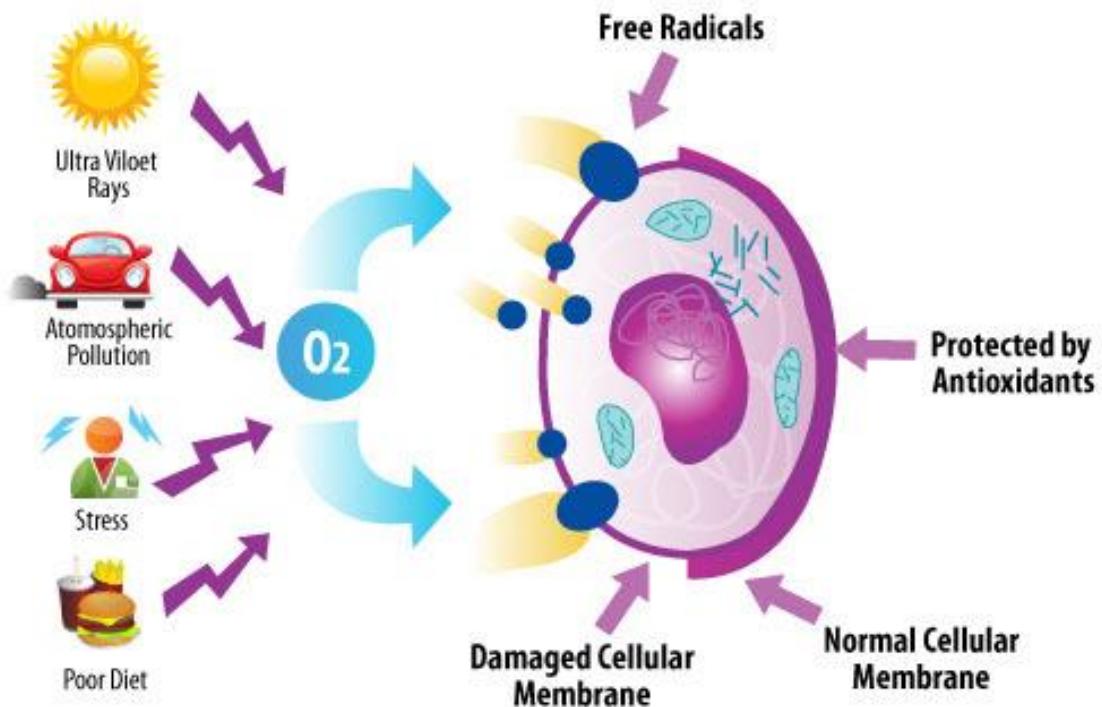
Total:



Western Blot

Modification:

Oxidative Stress



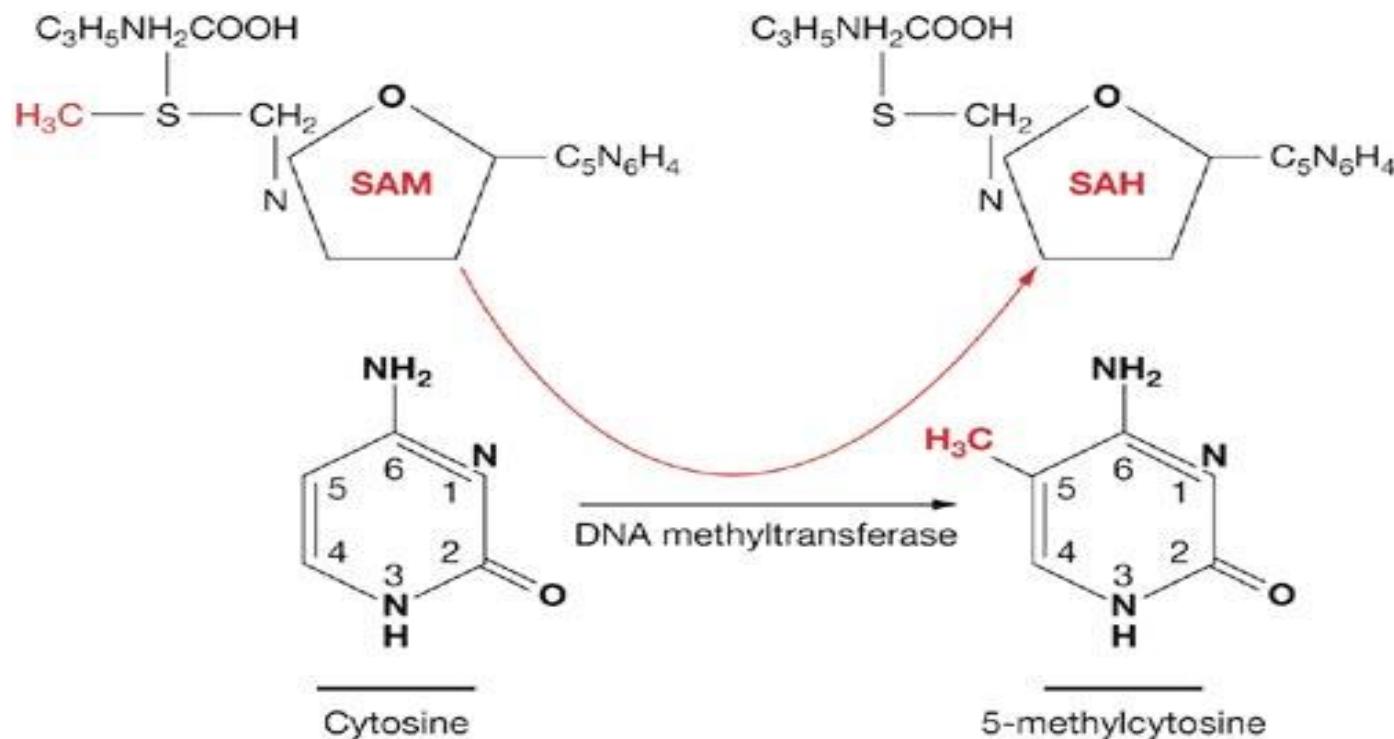
DNA Hypomethylation

DNA Methylation

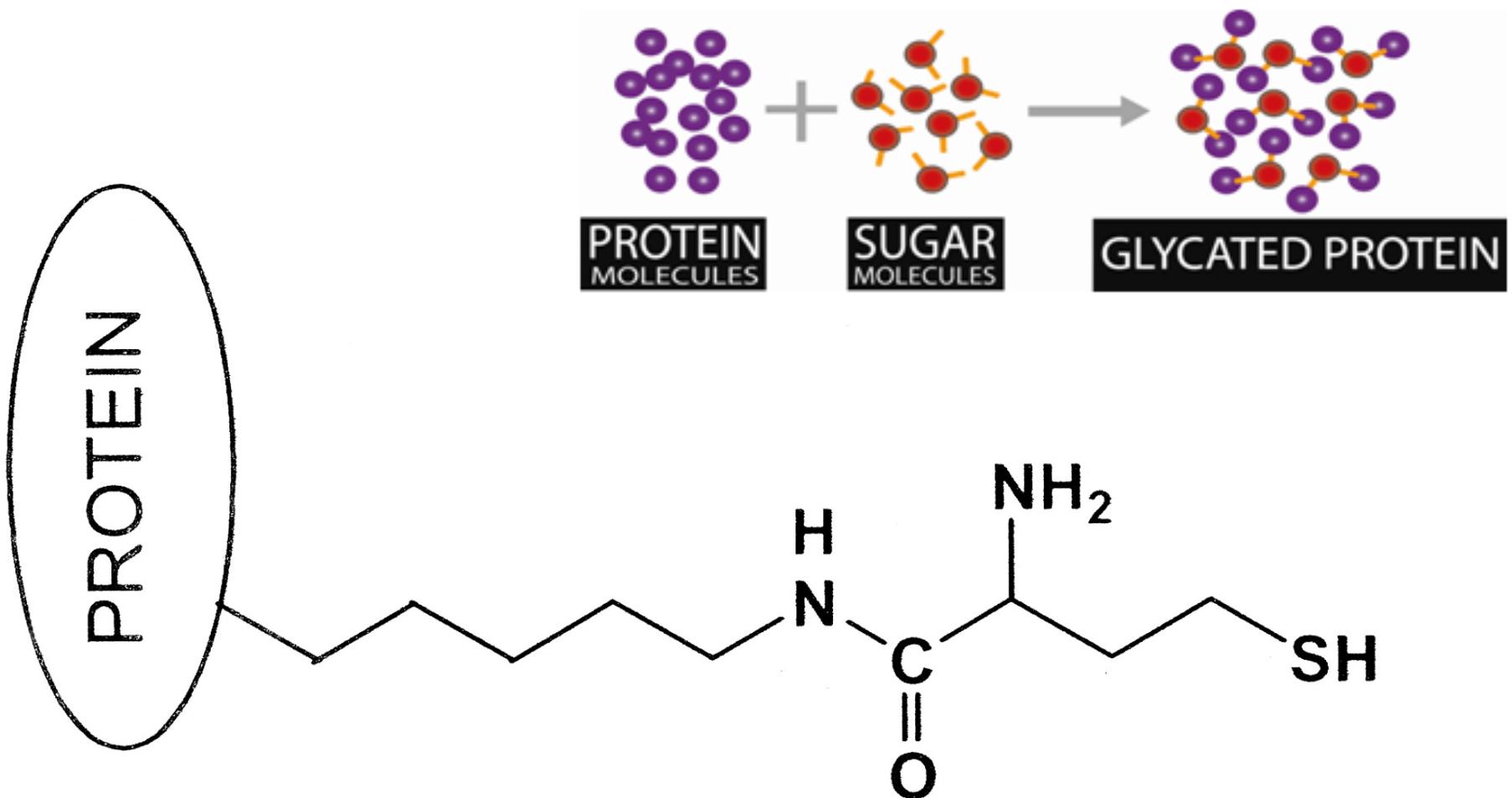
Gene Expression

Inactive Genes

Active Genes



N-homocysteinylation versus glycation !!



B) Dietary Bioactive Agents

Nutritional supplementation with novel dietary bioactive agents

Components in dietary active agents thought to be associated with the reduction of oxidative stress include:

- Antioxidant nutrients (vitamins C, E, Selenium, β -carotene)
- Phytonutrients (polyphenols, flavonoids, anthocyanin, carotenoids)



Date-Pits



Date-Pits-Oil



Date-Pits-Extract



Pomegranate Peel-Extract



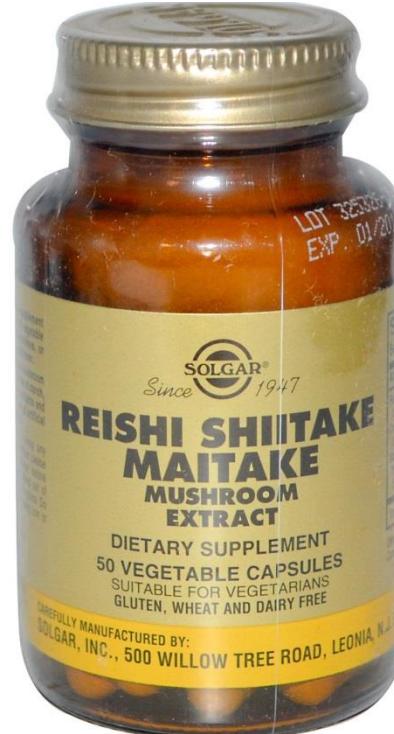
Seaweed



Freeze-Dried Extracts



Mushroom Extracts



Curcumin Extract



Garlic Extract



Emodin Extract



C) Colorectal Cancer

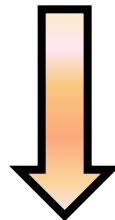
The global new pattern of life style and food habits is associated with an increased risk of non-communicable diseases colorectal cancer (CRC).

It has been suggested that CRC will continue to drain human and financial resources, if appropriate strategies are not developed and introduced to current health care system for primary prevention and early diagnosis.

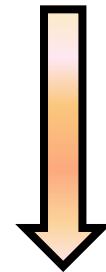
Primary Prevention of Hyperhomocysteinemia-mediated oxidative stress in relation to CRC

Low Status of Dietary antioxidants & B vitamins (Folate & Vitamins B6 and B12)

(Early Adulthood)



Hyperhomocysteinemia



Metabolic Triggers of CRC:

- 1) Oxidative stress: Glutathione depletion
- 2) DNA Hypomethylation: Low SAM/SAH ratio
- 3) N-protein homocysteinylation

Age Progress

Adulthood Stage

Research Findings (*in-vivo*, Experimental-based research at SQU)



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Abstract
Background
Methods
Results
Discussion
Conclusion
Competing interests
Authors' contributions
Acknowledgement

Research article

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Amelioration of azoxymethane induced-carcinogenesis by reducing oxidative stress in rat colon by natural extracts

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Abstract Send to: Asian Pac J Cancer Prev. 2013;14(9):5031-5.**Nabag (*Zizyphus spina-christi*) extract prevents aberrant crypt foci development in colons of azoxymethane-treated rats by abrogating oxidative stress and inducing apoptosis.**Guizani N¹, Waly MI, Singh V, Rahman MS.**⊕ Author information****Abstract**

Zizyphus spina-christi (ZSC) fruit is a rich source of bioactive compounds but any medicinal properties in chemoprevention of colon cancer have hitherto not been studied. The aim of the present study was to examine in vivo protective effects of ZSC water extract on colon carcinogenesis in azoxymethane (AOM)-treated rats. Our results showed that ZSC significantly reduced AOM-induced colonic aberrant crypt foci development and AOM-induced oxidative stress as indicated by restoration of endogenous glutathione depletion and abrogating the impairment of total antioxidant capacity. Caspase-3 cleavage, which has been considered as an apoptotic index, was almost undetectable in AOM-treated rats and ZSC exhibited pro-apoptotic effects evidenced by increased levels of cleaved caspase-3. In the studied model, our findings provide the first in vivo evidence that ZSC extract could inhibit the early stage of colon carcinogenesis by preventing oxidative stress and inducing apoptosis.

PMID: 24175771 [PubMed - in process] **Free full text**

Abstract

Send to:

Exp Biol Med (Maywood). 2011 Sep;236(9):1005-11. doi: 10.1258/ebm.2011.011010. Epub 2011 Jul 18.

Dietary folate protects against azoxymethane-induced aberrant crypt foci development and oxidative stress in rat colon.

Al-Numair KS¹, Waly MI, Ali A, Essa MM, Farhat MF, Alsaif MA.

Author information

Abstract

Azoxymethane (AOM) induces cancer and oxidative stress in rat colon. This study tested the hypothesis that dietary folate supplementation protects against AOM-induced oxidative stress and reduces aberrant crypt foci (ACF) development in rat colon. Fifty-four weanling male albino rats, with an average body weight of 50 ± 5 g, were randomly divided into three groups--A, B and C (18 rats per group)--and fed 2, 8 or 40 mg of folic acid per kg of supplemented diets, respectively, throughout the eight weeks' experimental period. The animals were supplied with diet and water ad libitum for four weeks and they reached an average body weight of 100 g. Thereafter each group was then further randomly subdivided into three subgroups (six rats per subgroup): control, vehicle and AOM-injected groups. The control group did not receive any treatment (neither AOM injection nor saline), the rats in the vehicle group were given 1 mL intraperitoneal injection of saline once a week for two weeks and the rats in the AOM-injected group were given two intraperitoneal injections of AOM dissolved in saline once a week for two weeks totaling 30 mg/kg body weight. After the last AOM injection, animals were continuously fed ad libitum their specified diet for two weeks of last AOM injection, all rats were sacrificed, and colon tissues were collected and used for ACF enumeration and measurements of glutathione (GSH) and total antioxidant capacity (TAC). The results revealed that AOM-injected rats showed lower levels of GSH and TAC as compared with control and vehicle groups. Folic acid-supplemented diets suppressed the AOM-induced ACF and GSH depletion in a dose-dependent manner and augmented the TAC. It was concluded that folic acid supplementation protects against the AOM-induced ACF formation by suppressing the AOM-induced GSH depletion in rat colon cells.

PMID: 21768165 [PubMed - indexed for MEDLINE]

Abstract Send to: [Asian Pac J Cancer Prev.](#) 2012;13(8):4051-5.**Pomegranate (*Punica granatum*) peel extract efficacy as a dietary antioxidant against azoxymethane-induced colon cancer in rat.**[Waly MI¹](#), [Ali A](#), [Guizani N](#), [Al-Rawahi AS](#), [Faroog SA](#), [Rahman MS](#).**⊕ Author information****Abstract**

Functional foods include antioxidant nutrients which may protect against many human chronic diseases by combating reactive oxygen species (ROS) generation. The purpose of the present study was to investigate the protective effect of pomegranate peel extract (PPE) on azoxymethane (AOM)-induced colon tumors in rats as an in vivo experimental model. Forty Sprague-Dawley rats (4 weeks old) were randomly divided into 4 groups containing 10 rats per group, and were treated with either AOM, PPE, or PPE plus AOM or injected with 0.9% physiological saline solution as a control. At 8 weeks of age, the rats in the AOM and PPE plus AOM groups were injected with 15 mg AOM/kg body weight, once a week for two weeks. After the last AOM injection, the rats were continuously fed ad-libitum their specific diets for another 6 weeks. At the end of the experiment (i.e. at the age of 4 months), all rats were killed and the colon tissues were examined microscopically for lesions suspected of being preneoplastic lesions or tumors as well as for biochemical measurement of oxidative stress indices. The results revealed a lower incidence of aberrant crypt foci in the PPE plus AOM administered group as compared to the AOM group. In addition, PPE blocked the AOM-induced impairment of biochemical indicators of oxidative stress in the examined colonic tissue homogenates. The results suggest that PPE can partially inhibit the development of colonic premalignant lesions in an AOM-induced colorectal carcinogenesis model, by abrogating oxidative stress and improving the redox status of colonic cells.

PMID: 23098515 [PubMed - indexed for MEDLINE]

Free full text

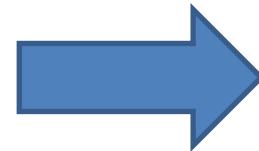
Take Home Message

“Dietary bioactive agents prevent hyperhomocysteinemia-mediated oxidative stress in CRC-induced models”

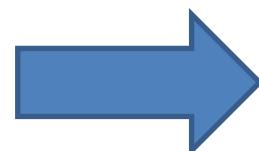
Novel Markers for Hyperhomocysteinemia Measurements



Invasive measurement



Non Invasive by measuring
Urinary 5 -Formyl Tetrahydrofolate



Questions

