

Saffron: A Promising Natural Gastrointestinal Drug!

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Director of NGS lab

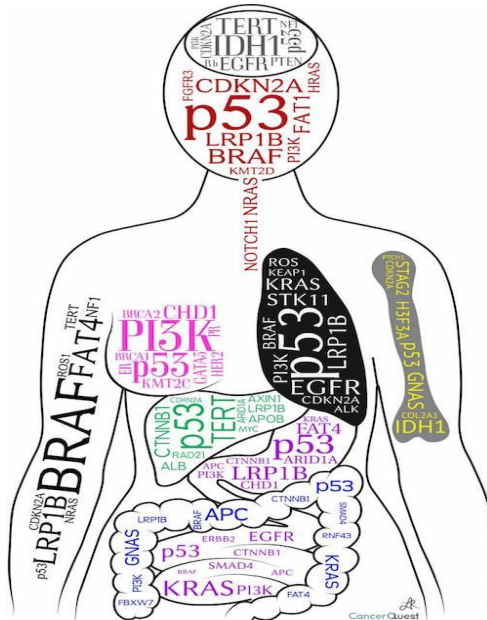
March 15, 2019, 2:30 PM

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Human Genome

Human Microbiome



Jon Be

Vermont

Famous people in Vermont

- Susan Bennett, 69. Voice Actress.
- Calvin Coolidge (1872-1933) US President.
- Joseph Smith (1805-1844) Religious Leader.
- Alex Farnham, 31.
- John Deere (1804-1886)
- Aaron Lewis, 46.
- Chester A. Arthur (1829-1886) US President.



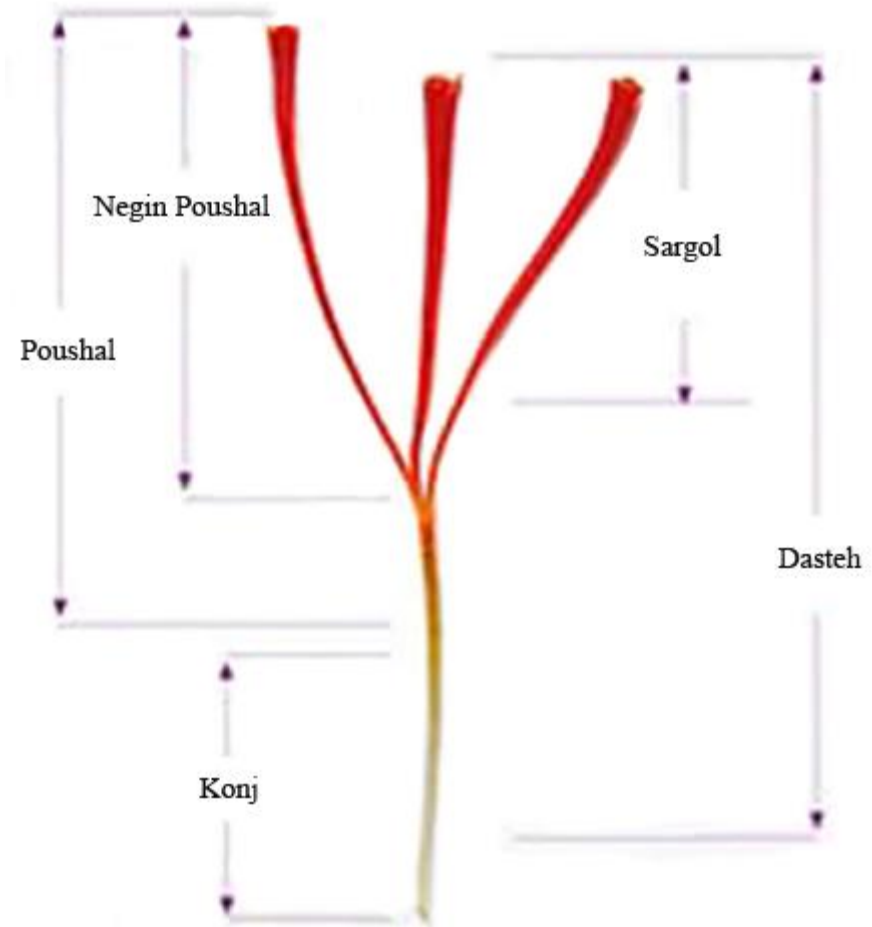
**Cheddar cheese,
Maple syrup,
the ever-popular Ben and Jerry's ice cream**



NIH is made up of 27 Institutes and Centers, each with a specific research agenda, often focusing on particular diseases or body systems.



Saffron types



Overall color of Sargol saffron is more than others and is between 210 to 260 units.

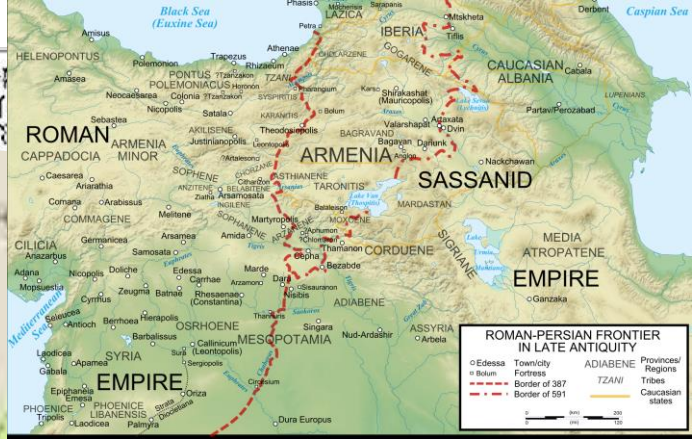
Table 1. Saffron world production

| Country | Production (kg) | Cultivated area (ha) | Ref. |
|-------------|-----------------|----------------------|---------------------------------|
| Iran | 160,000 | 47,000 | Ehsanzadeh et al., 2004 |
| India | 8,000 – 10,000 | n.a. | Fernandez, 2004 |
| Greece | 4,000 – 6,000 | 860 | Fernandez, 2004 |
| Azerbaijan | n.a. | 675 | Azibekova and Milyaeva, 1999 |
| Morocco | 1,000 | 500 | Ait-Oubahou and El-Otmani, 1999 |
| Spain | 300-500 | 200 | Fernandez, 2004 |
| Italy | 120 | 35 | Gresta et al., 2008 |
| France | 4 | 1 | Girard and Navarrete, 2005 |
| Turkey | 10 | n.a. | Thiercelin, 2004 |
| Switzerland | 0.4 | n.a. | Negbi, 1999 |

n.a. = not available.

Cyrus Cylinder

2600-year old symbol of Human Rights



Persian Empire
Professor John Lee
University of Santa Barbara

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Saadi Shirazi (1200-1292)



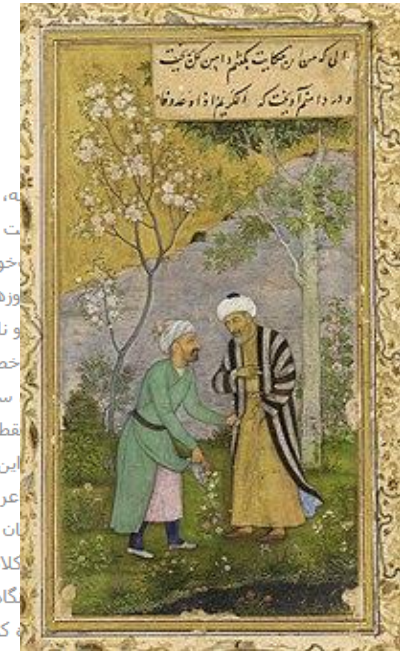
The Bostan and [The Golestan of Saadi](#) ,One of the world's greatest masterpieces

Saadi was born in Shiraz around 1200. He died in Shiraz around 1292. He lost his father in early childhood. With the help of his uncle, Saadi completed his early education in Shiraz. Later he was sent to study in Baghdad at the renowned Nezamiyeh College, where he acquired the traditional learning of Islam.

Human beings are members of a whole,
In creation of one essence and soul.
If one member is afflicted with pain,
Other members uneasy will remain.

If you have no sympathy for human pain,
The name of human you cannot retain.

| | |
|-------------------------------------|-----------------------------------|
| که سرمه‌ای چو دانی است کار | برو کار می‌کن، سگ چیست کار |
| به فرزندان چون همی خواست خفت | نگر تا که دهقان دانا چه گفت |
| که گنجی ز پنهانان اندر اوست | « که میراث خود را بهارید دوست |
| بزوهین و باقن با شمامت | من آن را نفاستم اندر کجاست |
| همه جای آن زیر و بالاکنید | چو شد مهر سه، کشنگه برکنید |
| بگریزد از آن گنج هر جا سراغ | نماند ناکنده جایی ز باغ |
| به گویین دشت بردند رنج | بدر مرد و پوران به امید گنج |
| هم اینجا، هم آنجا و هر جا که بود | به گواهن و بیل کشند زود |
| ز هر تنم برخاست هفتاد تنم | کشا را در آن سال از آن خوب ششم |
| چنان چون پند گفت، شد گنجشان | نشد گنج پیدا ولی زنجشان |



به، به واسطه حضور چشمگیر در متن جامعه که از قضا نقطه افتراق
ت و ساده‌زیستی اخلاق‌مدارانه دعوت می‌کند و از زیاده‌خواهی
خور عارفان که فرهنگ‌ساز و میراث‌دار جامعه‌ای است که اندک زمانی
وزها شاید، در رفت و آمد حاکمان است، که سعدی را به تاثیر از ابن
و ناگزیرش می‌سازد که مشفقانه سخن از چیزی گوید که در اصطلاح
خصوص می‌گوید: با در نظر گرفتن این سخن، «گرت مملکت باید
سعدی اصول مدیریت را هم مورد توجه قرار داده و شایسته‌سالاری
قط در اندیشه که در قامت یک اصلاحگر عملگرا، همزمان به حاکمان و
این نوع موضوعات حساس می‌سازد. استفاده مناسب از منابع
عر کهن بسیار ظریف گنجانده شده: «تخواهی که ضایع شود روزگار/
ان به مقدرات الهی و رسیدن رزق از سوی خدا، در شعر سعدی هم
کلاسیک، ایرانیان را به کار تشویق می‌کند و می‌گوید: «گرچه بیرون ز
گاه سعدی ظریف تر و دقیق‌تر از سایر شاعران کلاسیک کشور است،
کرده و جنبه‌های ظریفی را مطرح کرده است که در شعر شاعران

Nasir Al-Mulk Mosque in Shiraz, Iran

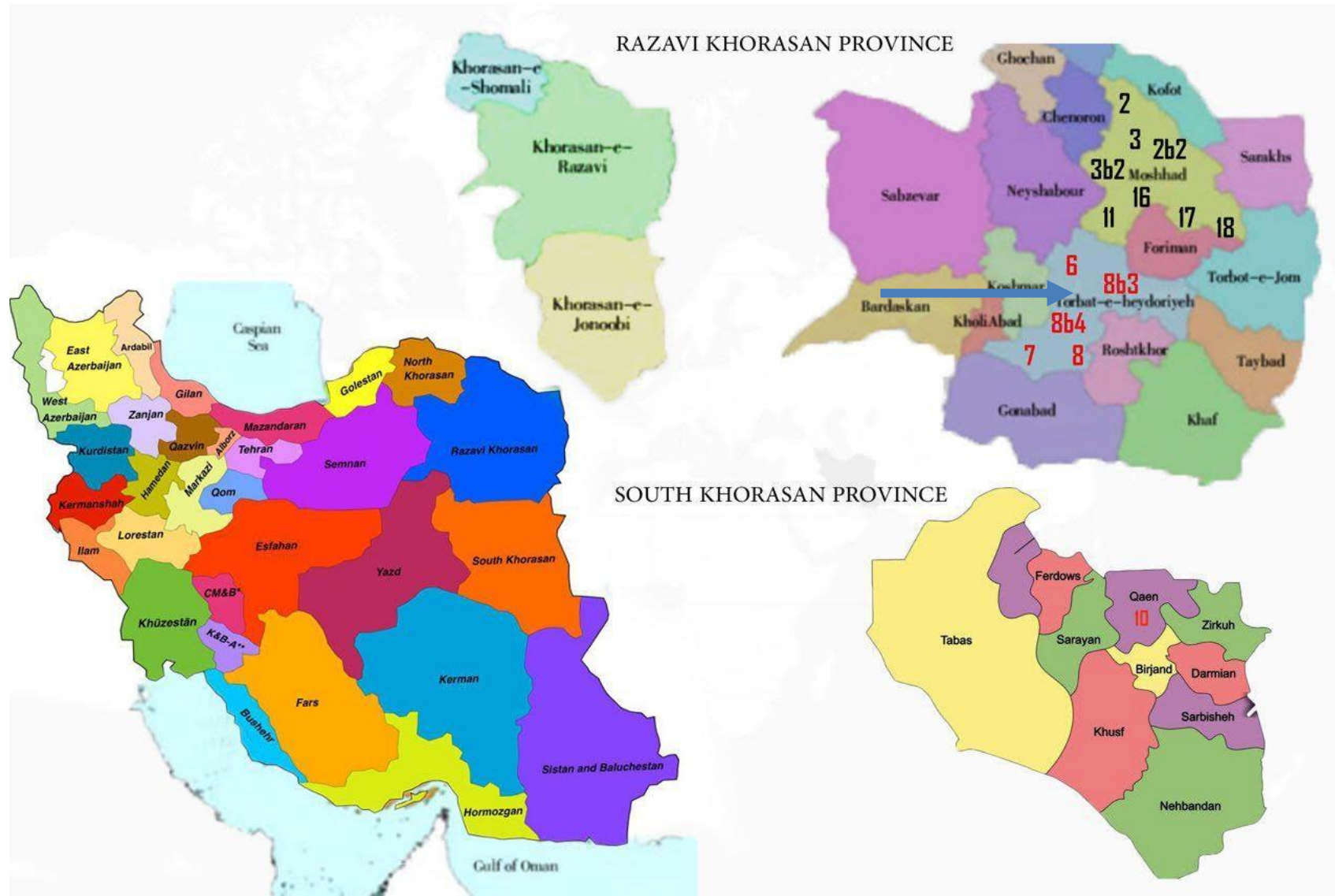


The Nasir al-Mulk Mosque (Persian: مسجد نصیر الملک - Masjed-e Naseer ol Molk) or Pink Mosque is a traditional mosque in Shiraz, Iran, located in Goade-e-Araban place (near the famous Shah Cheragh mosque). The mosque was built during the Qajar era, and is still in use under protection by Nasir al Mulk's Endowment Foundation. It was built by the order of Mirza Hasan Ali Nasir al Molk, one of the lords of the Qajar Dynasty, in 1876 and was finished in 1888. The designers were Muhammad Hasan-e-Memar and Muhammad Reza Kashi Paz-e-Shirazi.

The mosque extensively uses colored glass in its facade, and it displays other traditional elements such as panj kâseh-i (five concaves) in its design. It is also named in popular culture as Pink Mosque due to the usage of beautiful pink color tiles for its interior design.



Saffrons in Iran



Which country is the largest producer of saffron in the world

Iran

Ranks first in the world production of saffron in the world, with more than 94 percent of the world yield, exports the spice to 46 countries all over the world. Apr 27, 2012

Other minor producers of saffron are:

Spain, India, Greece, Azerbaijan, Morocco, and Italy.



Best saffron in the world



Saffron varieties are found throughout the world: including Iran, Spain, Morocco, Greece, India, and Italy.

Please visit **our poster** for the geography typing and quality of saffron.

Table 1. *Saffron Nutritional value per 100 gr

| Principle | Nutrient Value |
|----------------------|-----------------------|
| Energy | 310 Kcal |
| Carbohydrates | 65.37 g |
| Protein | 11.43 g |
| Total Fat | 5.85 g |
| Cholesterol | 0 mg |
| Dietary Fiber | 3.9 g |
| Vitamins | |
| Folates | 93 µg |
| Niacin | 1.46 mg |
| Pyridoxine | 1.010 mg |
| Riboflavin | 0.267 mg |
| Vitamin A | 530 IU |
| Vitamin C | 80.8 mg |
| Electrolytes | |
| Sodium | 148 mg |
| Potassium | 1724 mg |
| Minerals | |
| Calcium | 111 mg |
| Copper | 0.328 mg |
| Iron | 11.10 mg |
| Magnesium | 264 mg |
| Manganese | 28.40 mg |
| Phosphorus | 252 mg |
| Selenium | 5.6 µg |
| Zinc | 1.09 mg |

***USDA**

Table 2. Saffron Constituents and their responsibilities

| Constituent | Responsible | Action |
|--------------------|--------------------|---------------|
| Crocin | color | Anti-disease |
| Picrocrocin | bitter taste | Anti-disease |
| Safranal | Aroma | Anti-disease |

Anti-disease=fight sickness



The Components of the Digestive System

Burden of Colorectal Cancer (CRC)

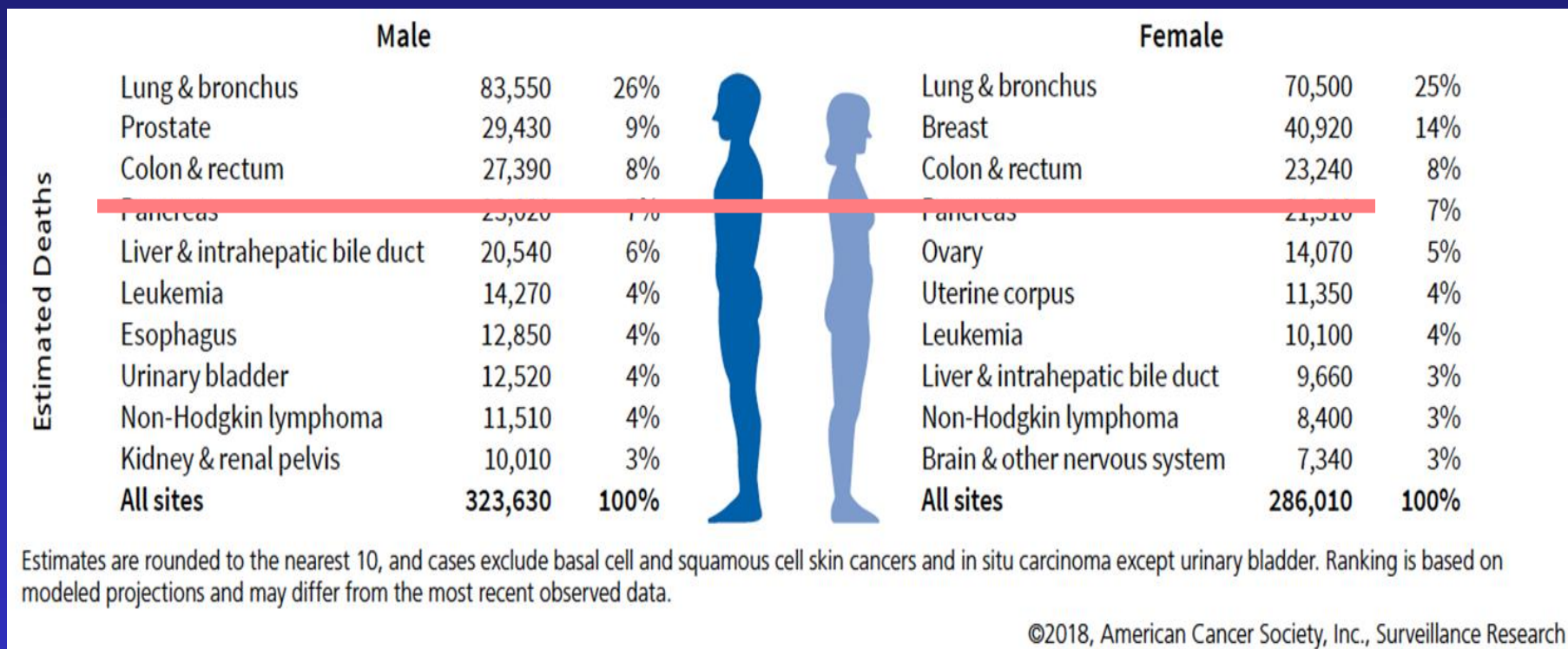
- World-wide about 1,400,000 people are diagnosed with colorectal cancer each year
- 2.4 million cases of CRC diagnosed every year by 2035.
- Both women and men
- All races
- Second leading cause of cancer death in US
- American Cancer Society estimates in 2019
 - 97,220 new cases
 - 50,000 deaths
 - About 27,400 patients will have had their cancer metastasiz.*



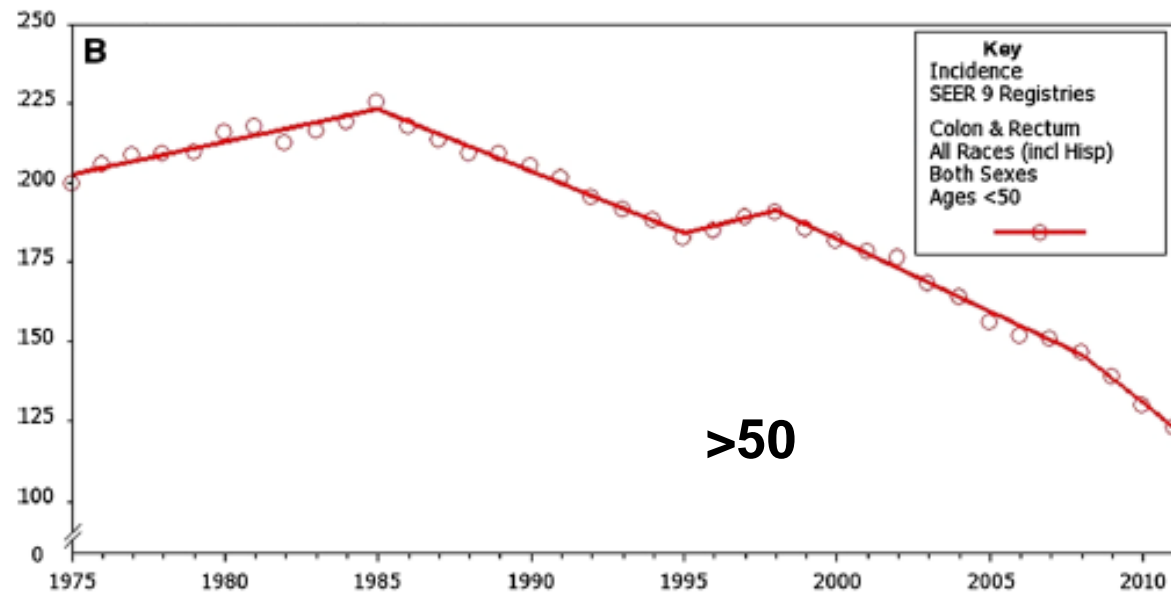
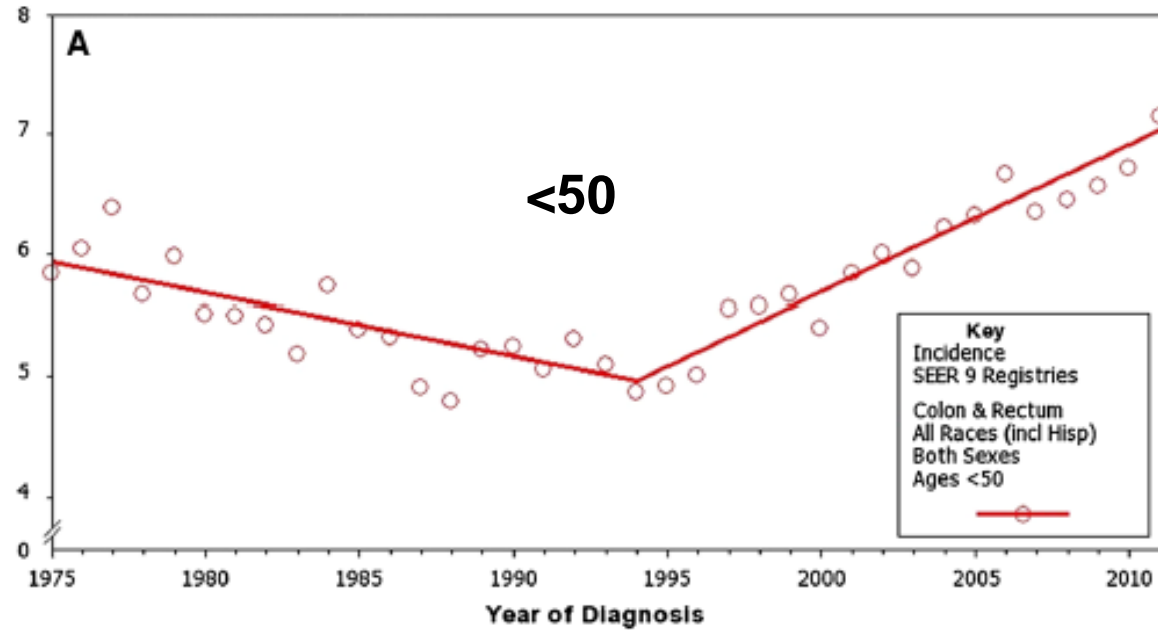
*National Cancer Institute; Surveillance, Epidemiology, and End results Program Fact Sheet: Colon and Rectum. <http://seer.cancer.gov/statfacts/html/colorect.html>. Accessed April 2018.

**<https://www.wcrf.org/int/cancer-facts-figures/data-specific-cancers/colorectal-cancer-statistics>

Ten Leading Cancer Types for the Estimated New Cancer Deaths, by Sex, US, 2018.



Colorectal Cancer in Young Adults



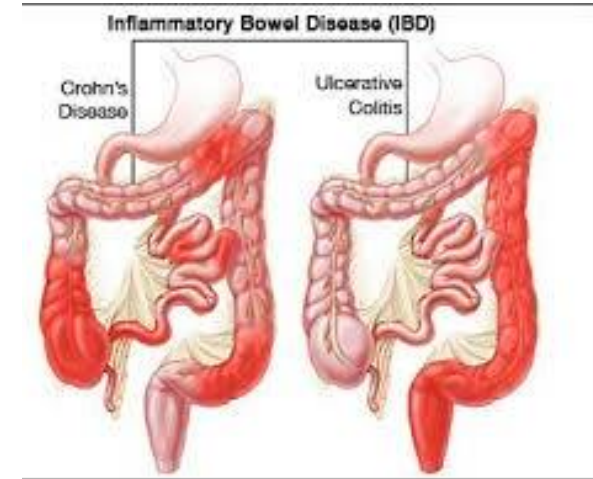
Dig. Dis Sci 2015, 60:722

Time trend of CRC incidence in USA. Modified from the NCI web site. A) Age <50, B) age >50.

Ashktorab et al 2016. Dig Dis Sci. 2016 Oct;61(10):3026-30. doi: 10.1007/s10620-016-4207-1.

Gastrointestinal (GI) diseases in the US (per year)

- About 60-70 million
- In 2004,
 - An estimated 4.6 million hospitalizations
 - 72 million ambulatory care visits
 - 236,000 deaths
- Spending on GI diseases
 - An estimated at \$142 billion



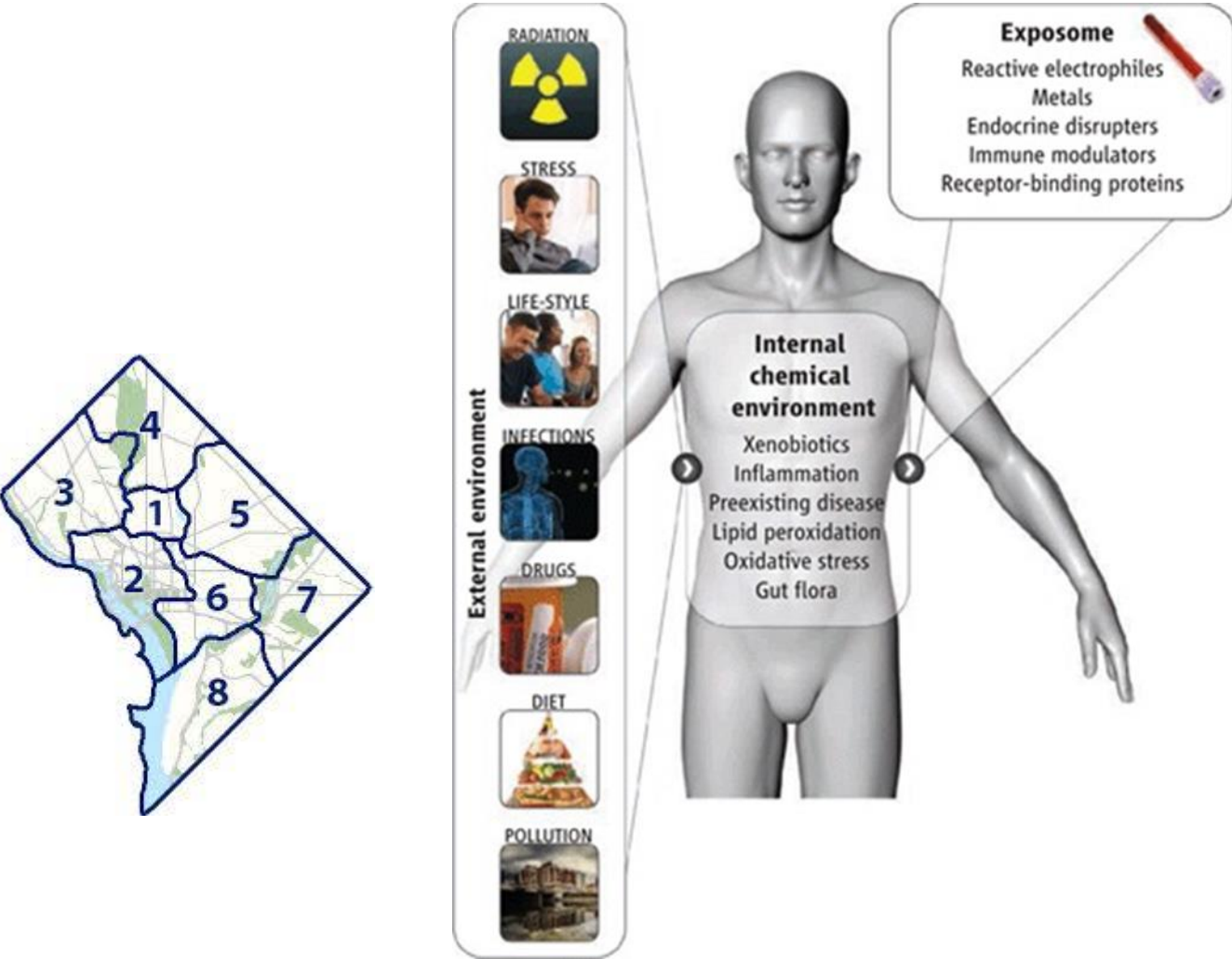
Saffron



The anti-cancer activity of saffron components seems to occur indirectly through

- **Anti-oxidant**
- **Anti-inflammatory action**
 - **Directly through their anti-proliferative and proapoptotic effects.**

Environmental exposure



DC has the different life expectancy based on wards

Saffron and protection against diseases



Microbiome and colon disease



GUT Brain axis
GUT and Joint axis
GUT and body axis

Microbiome and Organes

Mild Colitis

- ✓ **Colitis is a global disease with increasing incidence and prevalence worldwide and with different frequencies dependent on age, ethnical background and geographic localization.**
- ✓ **Prevalence rates for Colitis range from 90 to 505 per 100,000 persons in Northern Europe and Northern America.**
- ✓ **Among Caucasians the highest annual incidence of Colitis is 24.3 per 100,000 person-years in Europe and 19.2 per 100,000 person-years in North America.**
- ✓ **The disease is less common in Eastern and Southern Europe, and at least 10 times less common in Asian, African and Oriental populations.**
- ✓ **Rising incidence and prevalence have also been shown for these ethnic groups, suggesting additional environmental and lifestyle effects on the pathogenesis of Colitis.**
- ✓ **The female to male ratio for UC differs between 0.51 and 1.58 indicating that UC is not sex specific.**
- ✓ **Any age group from infants to the elderly can be affected, but the peak age of onset is between 15 and 30 years with a second but smaller peak between 50 and 70 years.**
- ✓ **20% to 30% of patients with Colitis and CD disease have the onset of their symptoms below the age of 18, although diagnosis is often delayed**

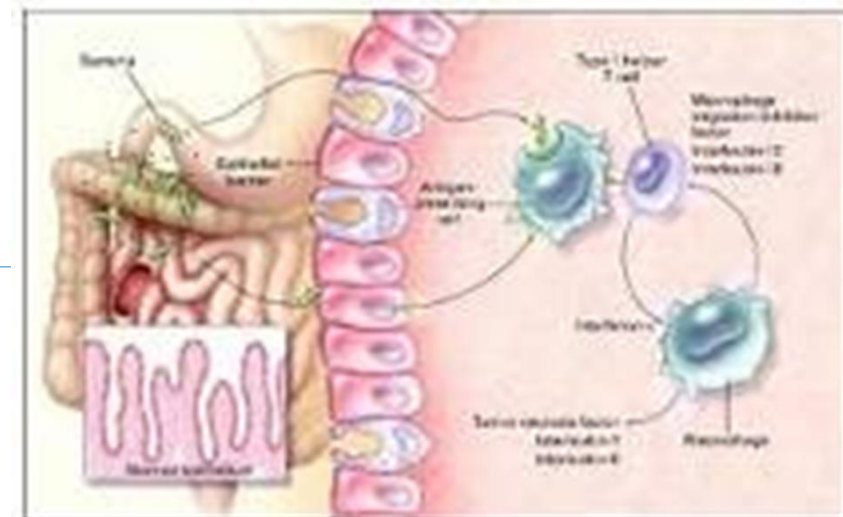
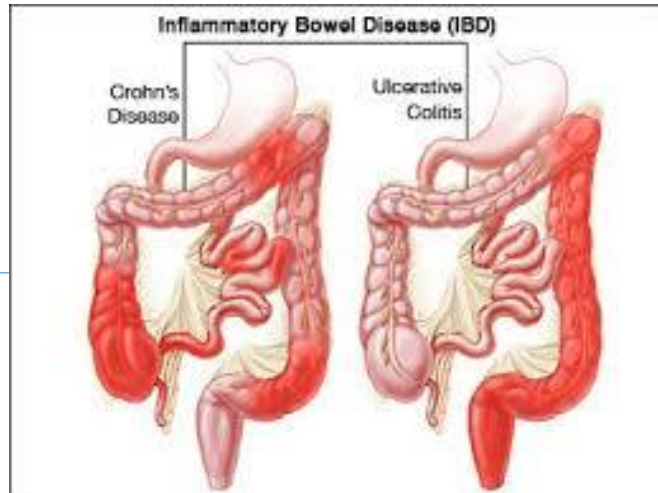
Mild Colitis

➤ Symptoms

- Ulcerative colitis symptoms can vary, depending on the severity of inflammation and where it occurs. Signs and symptoms may include:
- Diarrhea, often with blood or pus
- Abdominal pain and cramping
- Rectal pain
- Rectal bleeding — passing small amount of blood with stool
- Urgency to defecate
- Inability to defecate despite urgency
- Weight loss
- Fatigue
- Fever
- In children, failure to grow

Inflammatory Bowel Disease

- Inflammatory bowel diseases are a group of inflammatory conditions in which the body's own immune system attacks parts of the digestive system.
- The two most common inflammatory bowel diseases are Crohn's disease (CD) and ulcerative colitis (UC).
- IBD affects as many as 1.4 million Americans, most of whom are diagnosed before age 35. There is no cure for IBD but there are treatments to reduce and control the symptoms of the disease.



Inflammatory Bowel Disease (Causes)

- **The exact cause of IBD remains unknown.**
- **Researchers believe that a combination of four factors lead to IBD:**
 - Genetic component,
 - Environmental trigger,
 - Imbalance of intestinal bacteria
 - Inappropriate reaction from the immune system.
- **Immune cells normally protect the body from infection, but in people with IBD, the immune system mistakes harmless substances in the intestine for foreign substances and launches an attack, resulting in inflammation.**

Scope of IBD in USA

Estimated prevalence¹

- UC: 37-346:100,000
- CD: 26-199:100,000

Physician visits: >700,000/year²

Hospitalizations: 100,000/year²

Annual direct costs: ~\$4 billion³

1. Lichtenstein G. 2012. *Goldman's Cecil Medicine*. 24th ed. . Philadelphia, PA: Elsevier Saunders; 2012:913-921.

2. CDC. <http://www.cdc.gov/ibd/>. 2015.

3. Lichtenstein GR. *Am J Gastroenterol*. 2016.[Abstract 682]

Saffron aqueous extract (SFE) treatment increases the colon length and improves histopathological characteristics of colonic mucosa in DSS-induced colitis mice

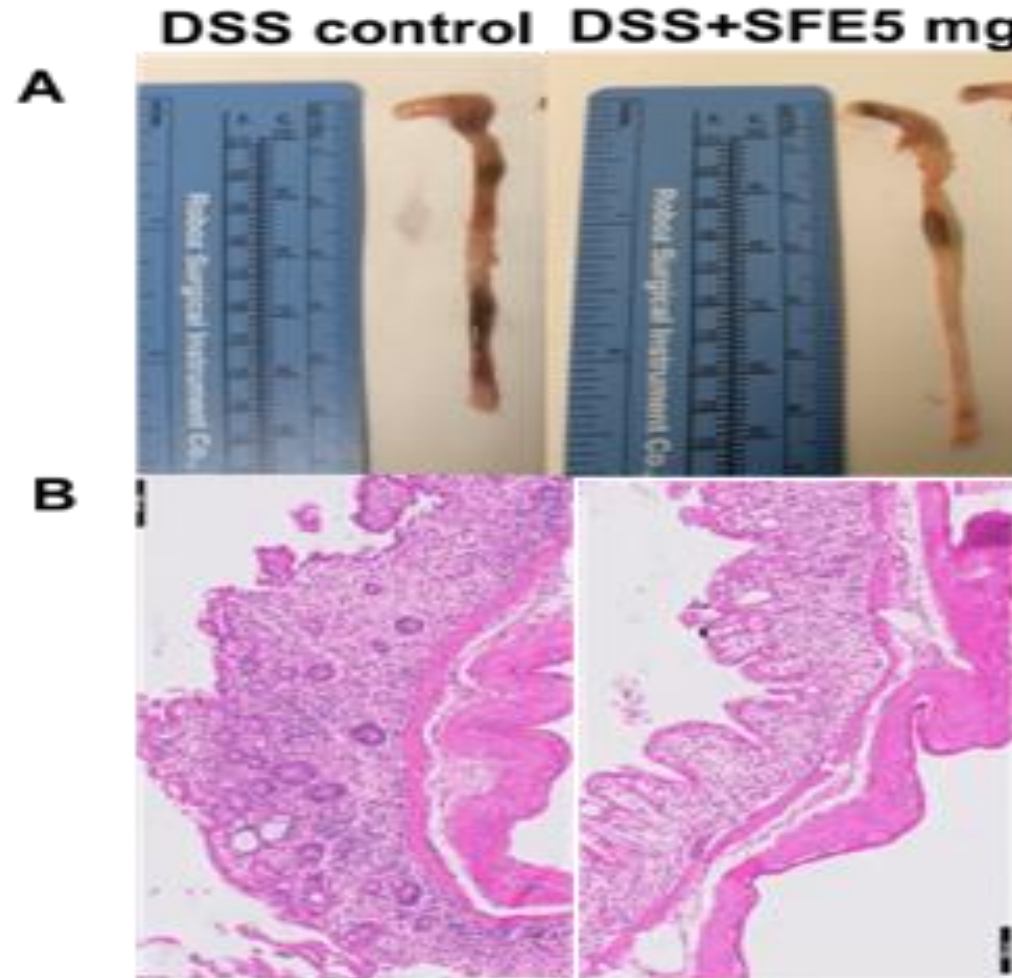


Figure 1: Colon Length and Histology of colon tissue

Irritable Bowel syndrome (Who Gets IBS?)

- IBS affects an estimated 10–15% of adults in the United States.
- Age.
 - The highest rates of IBS are seen in persons who are in middle adulthood, younger than 45.
- Gender.
 - The majority of those diagnosed with IBS are female.
- Family history.
 - Research shows that many people with IBS have a first-degree relative (parent, child or sibling) with the disorder.
- Psychological history.
 - Some studies indicate that psychological distress, especially anxiety, depression and childhood adversity, may be a risk factor.

Saffron components were shown to down-regulate several pro-inflammatory cytokines' expression. The effects of crocin and crocetin against oxidative stress include reduction of malondialdehyde level, improving the levels of glutathione and anti-oxidant enzymes such as superoxide dismutase, catalase and glutathione peroxidase, as well as reducing lipid peroxidation.

IBS INFOGRAPHIC

Irritable Bowel Syndrome

Symptoms



Constipation and Diarrhea



Colon pain



Mucus in the stool



Bloating



Relaxation



Diet



Medications



Exercises

Avoid



Lactose



Gluten

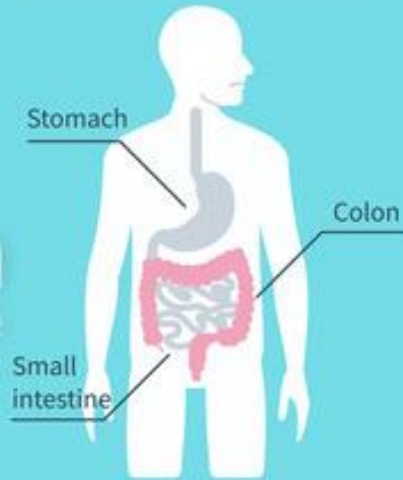


Fast Food



Alcohol

ANATOMY OF SMALL INTESTINE



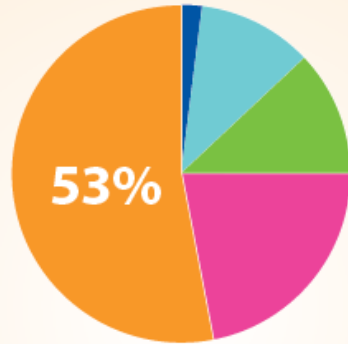
Helicobacter pylori



Microflora

#206006157

Irritable Bowel Syndrome (IBS)



**53% have suffered
with IBS for more
than 10 years**

41% have IBS-M
(mixed type)

35% have IBS-D
(diarrhea predominant)

18% have IBS-C
(constipation predominant)

6% aren't sure

Table1: Primary and secondary outcome measurements for the treatment with Saffron vs. Fluoxetine



| Questionnaire | Weeks into treatment | Treatment Group | | | | | |
|---------------|----------------------|---|------|-----------------|--|------|-----------------|
| | | saffron  | | | Fluoxetine  | | |
| | | Mean | SD | <i>p-value*</i> | Mean | SD | <i>p-value*</i> |
| IBS-Qol | Baseline | 60.00 | 9.15 | | 59.18 | 7.28 | |
| | 2 weeks | 60.61 | 8.07 | 0.033 | 59.27 | 6.21 | 0.753 |
| | 4 weeks | 62.36 | 7.27 | <0.001 | 61.33 | 6.74 | <0.001 |
| | 6 weeks | 68.06 | 7.00 | <0.001 | 67.36 | 7.58 | <0.001 |

Table 3. Molecular mechanisms by which extracts of saffron exert anti-cancer activity in GI cancers.

| Type of Cancer | Secondary Metabolite | Mechanism of action | Molecular Changes | References |
|-------------------|----------------------|---|---|----------------------------|
| Hepatic Cancer | crocin | Apoptosis | Down-regulation of hTERT gene Down-regulation of the expression of catalytic subunit of enzyme telomerase | 43, 44, 47 |
| | | Antioxidant Property and Anti-inflammatory effect | Increased the levels of GST, SOD and CAT Reduced myeloperoxidase activity, malondialdehyde Inhibition of COX 2, iNOS, NF-kB | |
| Pancreatic Cancer | crocetin | Cell cycle arrest at G2/M Phase | Reduced expression of Cdc-2 (hyperphosphorylation) Reduced expression of Cdc-25c phosphatase Inhibition of Cyclin B1 | 48 |
| | crocin, crocetin | Apoptosis | Increased expression of Bax protein Suppressed expression of Bcl-2 Elevated Bax/Bcl-2 ratio | 48-50 |
| | crocetin | Inhibition of cell proliferation | Reduced activity of EGFR Reduced phosphorylation of Akt | 48, 50 |
| Colorectal Cancer | crocetin | Cell cycle arrest at S Phase | Reduced expression of cyclin A and cdk2 | 51 |
| | crocin | Cell cycle arrest at G3 phase | Decrease in the levels of cyclin B1 and pH3 | 41, 44 |
| | crocin crocetin | Apoptosis | Augmented expression of p53 and P21 | 41, 52 |
| | crocin | DNA Damage | Up-regulation of H2AX | 41, 44 |
| | | Autophagolysis | Formation of LC3-II Decrease in protein levels of Beclin 1 and Atg 7 genes | 44 |
| Gastric Cancer | crocin | Apoptosis | Activation of caspases Elevated Bax/Bcl-2 ratio | 53 |

Similarities and Differences Between IBD and IBS

| | IBD | IBS |
|----------|---|--|
| SYMPTOMS | <ul style="list-style-type: none">• Frequent and/or urgent bowel movements• Diarrhea ★• Bloody stool• Abdominal pain and cramping ★• Fatigue• Lack of appetite• Weight loss• Joint, skin or eye problems | <ul style="list-style-type: none">• Abdominal pain and cramping ★• Bloating• Gas• Mucus in stool• Diarrhea and/or constipation ★ |

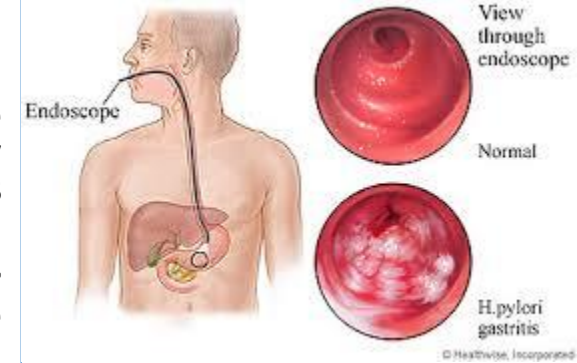
★ similarities

Chronic gastritis

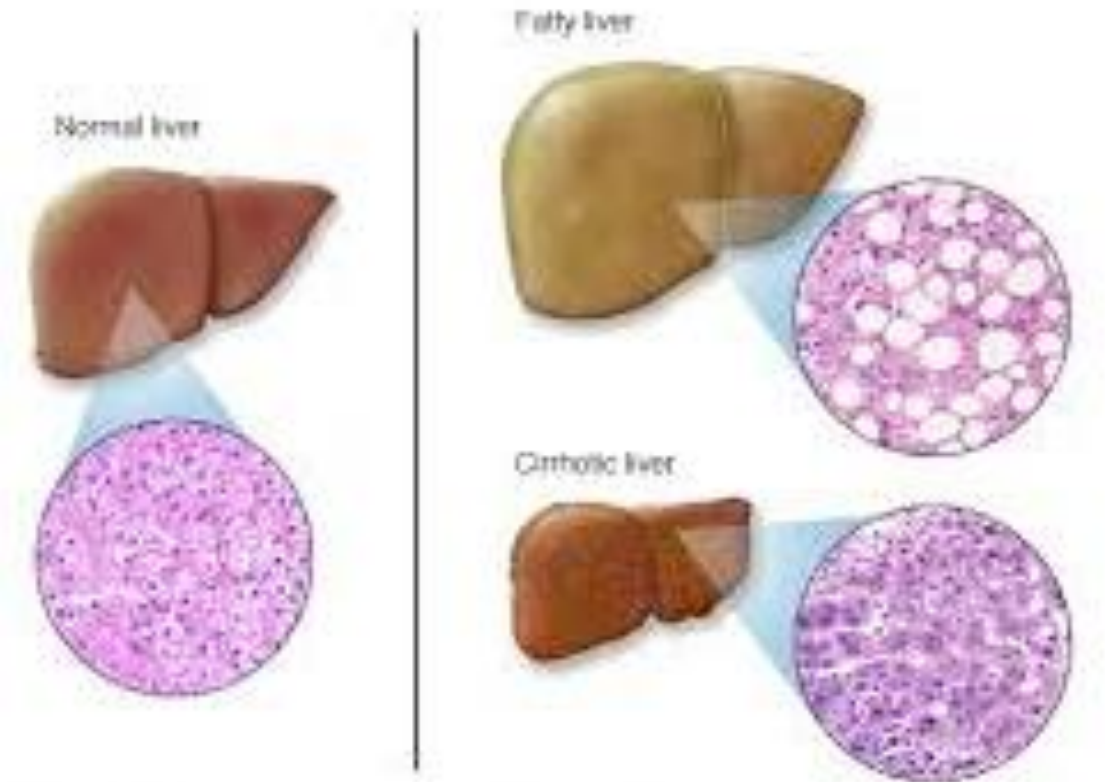
- Chronic gastritis is one of the most common life-long, serious and insidious illnesses in human beings.
- One may estimate that more than half of the world population have this disease in some degree and extent, indicating that even many hundreds of millions of people worldwide may have chronic gastritis in a form or other
- One may estimate that millions of premature deaths may occur annually worldwide due to cancer and ulcer as sequelae of the chronic gastritis
- Prevalence of chronic gastritis has markedly declined in developed populations during the past decades. However, chronic gastritis is still one of the most common serious pandemic infections with such severe killing sequelae as peptic ulcer or gastric cancer.

The study concluded that crocin protects rat gastric mucosa against ethanol-induced injury by displaying anti-inflammatory, anti-oxidative, anti-apoptotic and mucin-secretagogue mechanisms, probably mediated by increased mucosal prostaglandin E2 (PGE2) release. 20

Inoue et al. reported that saffron can inhibit ulcers that are induced by stress and histamines²². Similarly, Al-Mofleh also showed that saffron has significant anti-secretory and anti-ulcer activities ²³.



Liver Cancer Symptoms



- Most people don't have signs and symptoms in the early stages of primary liver cancer. When signs and symptoms do appear, they may include:
- Losing weight without trying
- Loss of appetite
- Upper abdominal pain
- Nausea and vomiting
- General weakness and fatigue
- Abdominal swelling
- Yellow discoloration of your skin and the whites of your eyes (jaundice)
- White, chalky stools



- **The average human has 100 trillion microbes in the gut**
- **10 times more than the cells in the human body**
- **Gut microbial genome is ~150 times larger than human genome**
- **The number and variety of bacteria increase from the proximal to the distal GI tract.**



Microbes promote gut maturity

Gastrointestinal Bacteria in Normal Humans

Stomach $0-10^2$

Lactobacillus
Candida
Streptococcus
Helicobacter pylori
Peptostreptococcus

Duodenum 10^2

Streptococcus
Lactobacillus

Distal Ileum 10^7-10^8

Clostridium
Bacteroides sp
Coliforms

Jejunum 10^2

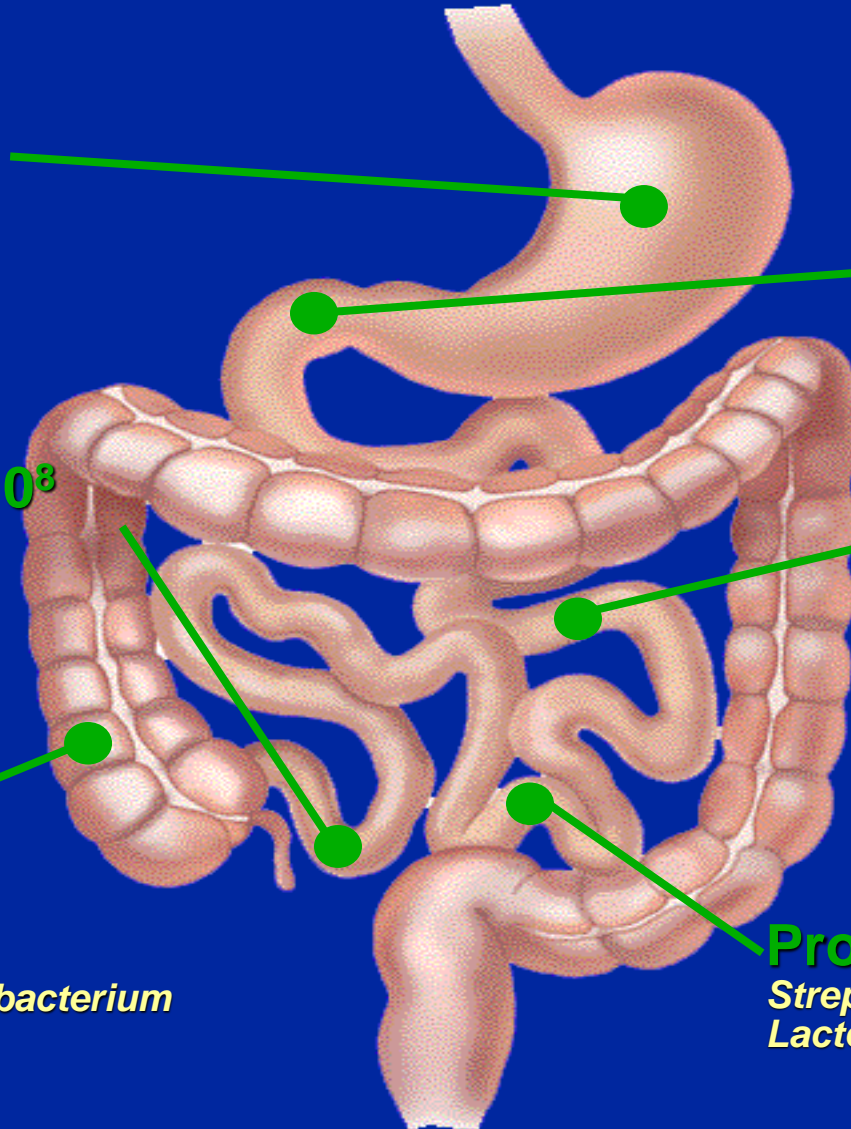
Streptococcus
Lactobacillus

Colon 10^{11}

Bacteroides
Bifidobacterium
Clostridium coccoides
Clostridium leptum/ Fusobacterium
Coliforms (10^8)

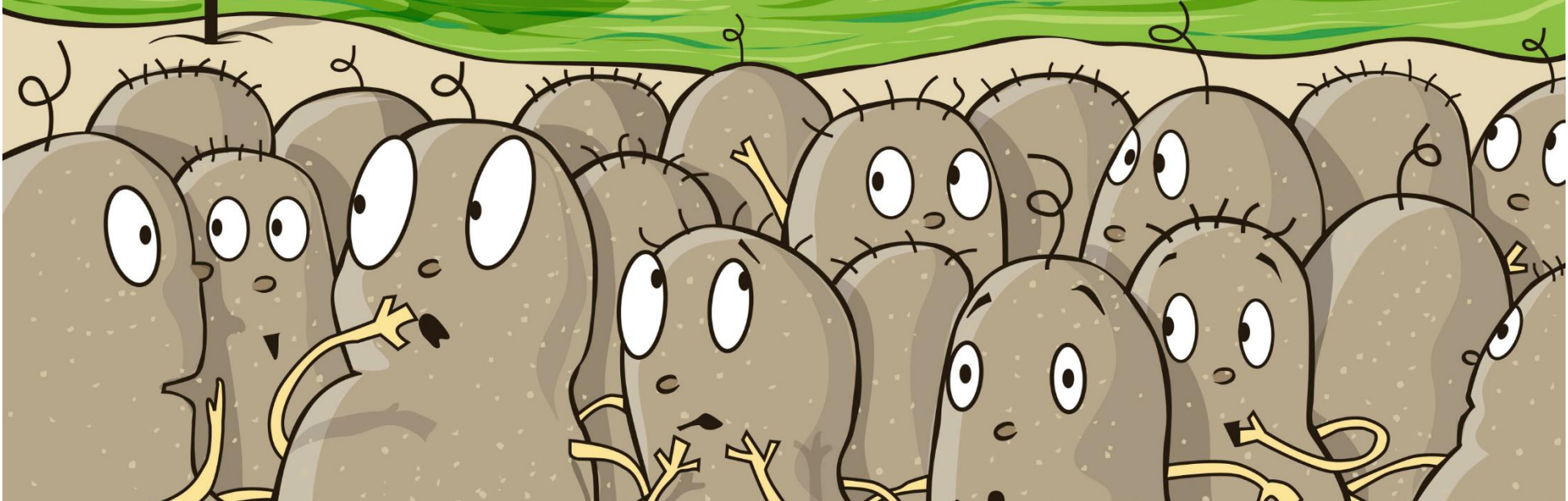
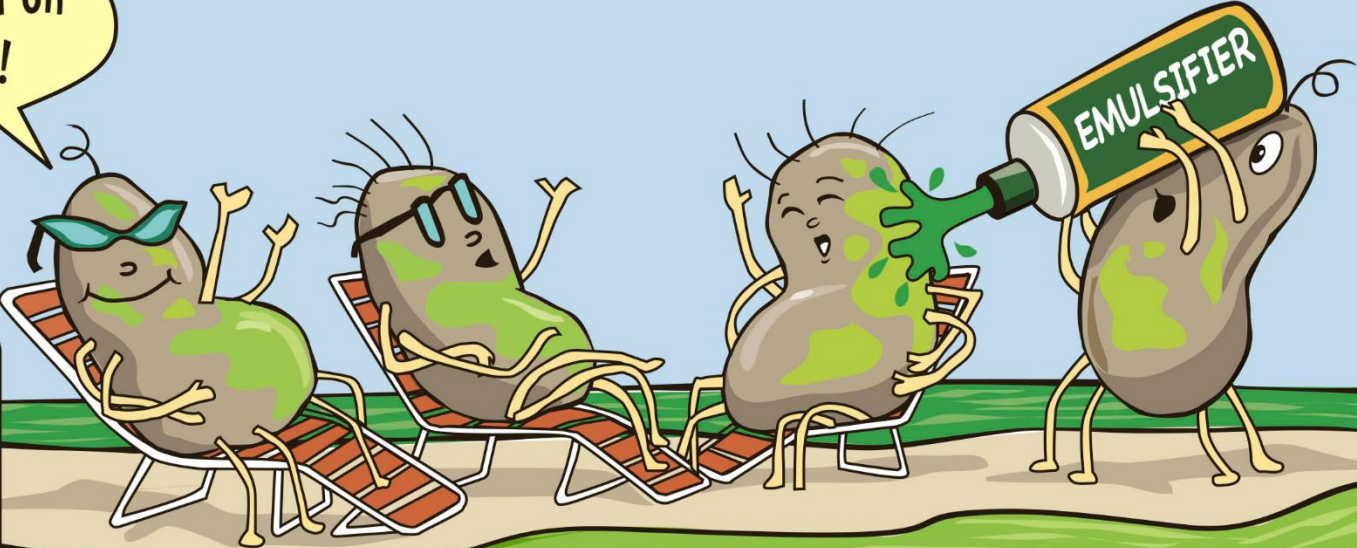
Proximal Ileum 10^3

Streptococcus
Lactobacillus



I love hanging out on the epithelium!

RESTRICTED AREA
KEEP OUT OF MUCUS



Dysbiosis-Associated Diseases or Conditions

Obesity

Metabolic syndrome

Nonalcoholic steatohepatitis

Inflammatory bowel diseases (Crohn's disease, ulcerative colitis, pouchitis)

Irritable bowel syndrome, functional bowel disorders

Atherosclerosis

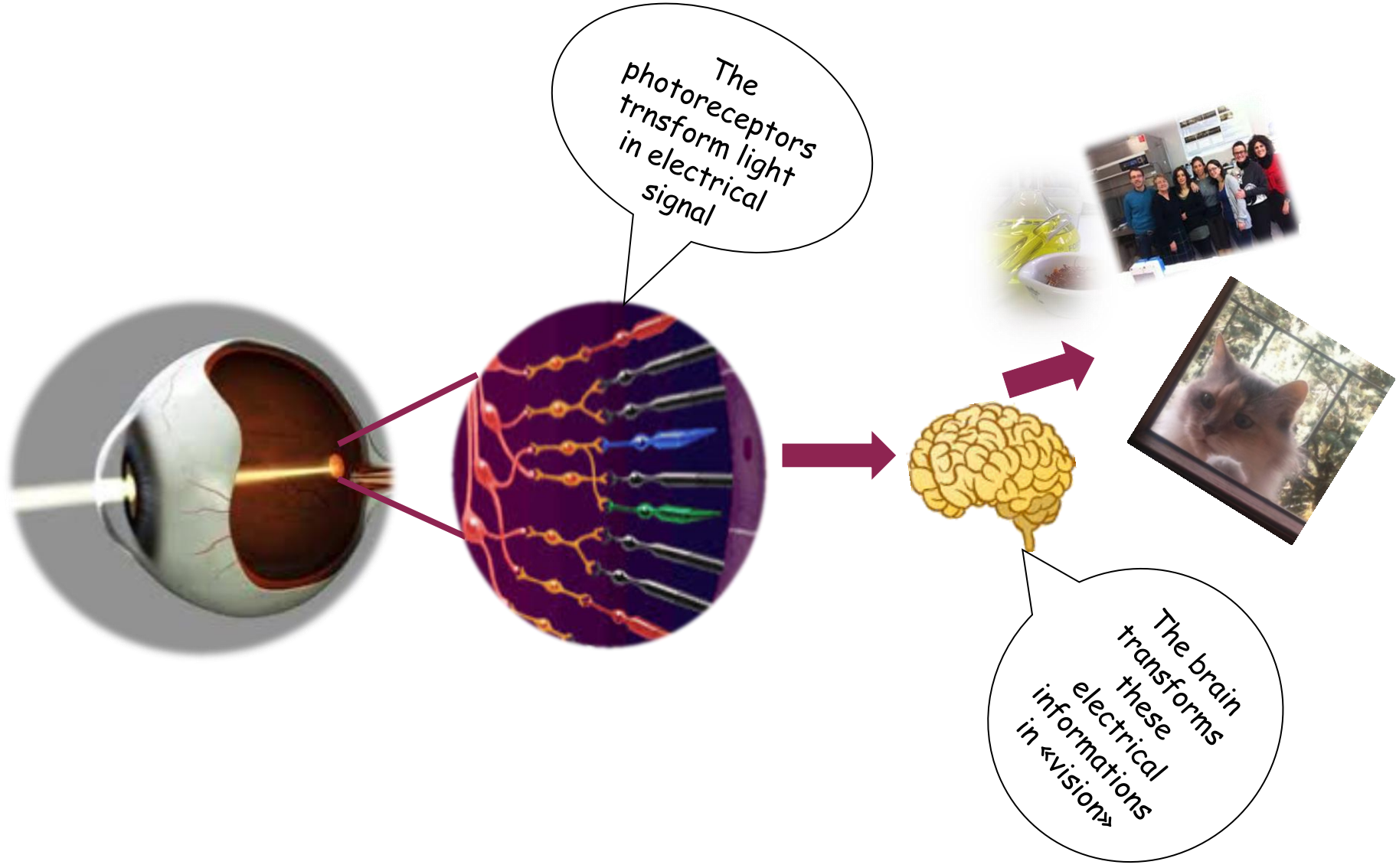
Type 1 diabetes

Autism

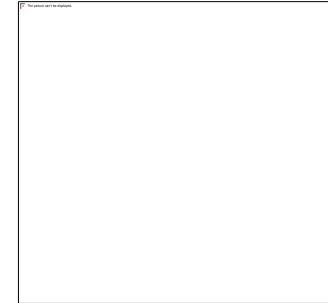
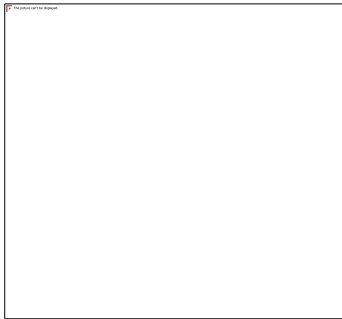
Allergy

Asthma

Celiac disease



The neurodegeneration of the retina lead to progressive loss of vision





Saffron Oral administration



Aged related Macular Degeneration'

In MEN

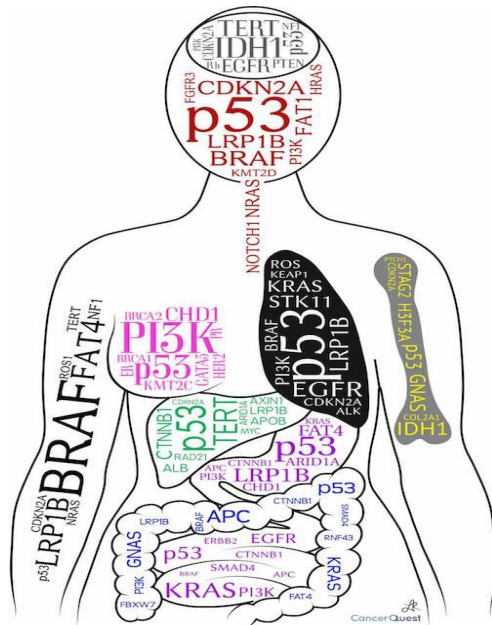
Saffron

GUT-body axis (brain, joint, eye,..)

- anti-inflammation
- dysbiosis
- anti-toxigenic bacteria
- Anti-ROS
- interventional on moderate



Does Saffron effect on our genome or Microbiome genome?



Precision medicine using Genome and Microbiota

Acknowledgements

Howard University

Brim

Tabtabaei

Soleimani

Italy

L'Aquila University

Bisti

Latella

Stanford University

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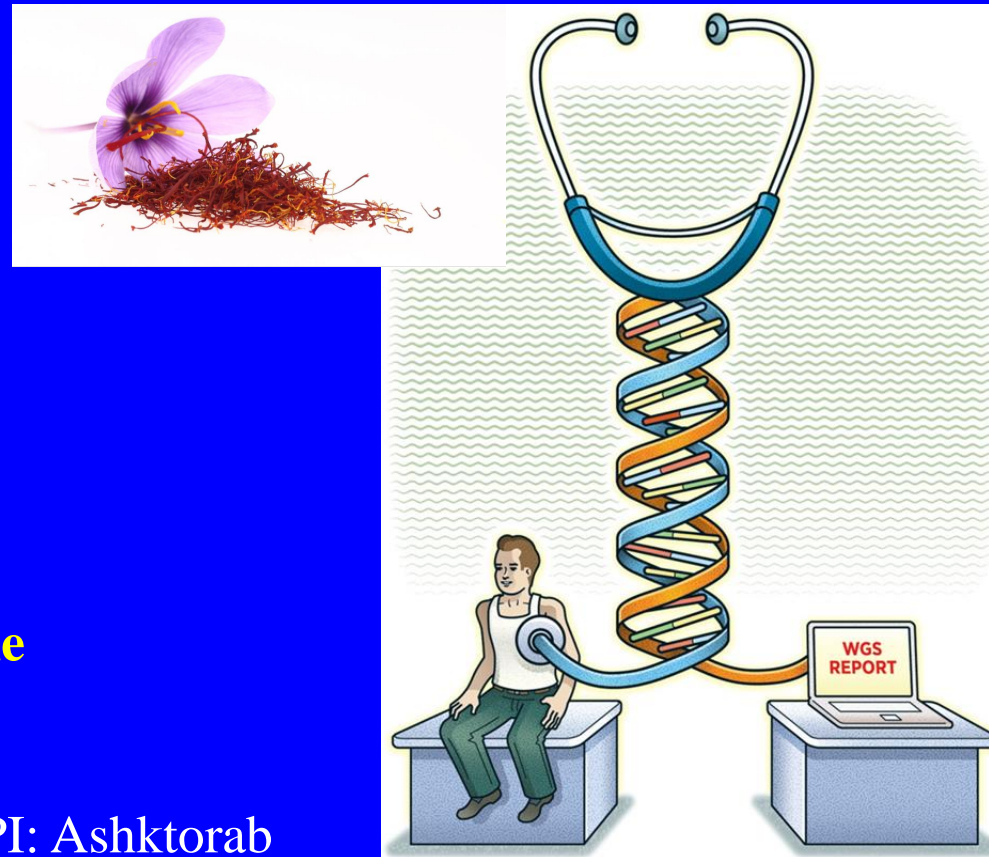
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HiThru Analytics

Varma

Zarin Saffron

Shoraka





Thank you

