Vermont

cheddar cheese,

maple syrup and

the ever-popular Ben and Jerry's ice cream and Now Saffron

Famous people in Vermont

Bernie Sanders

- JoJo, 28.
- 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.

Saffron as anti inflammatory and anti oxidant supplement

Hassan Ashktorab, Professor

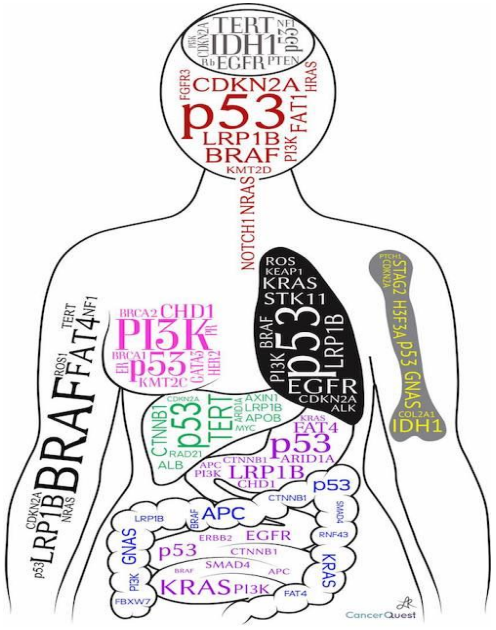
Director of NGS lab

March 12, 2020, 2:15 PM

University of Vermont, Davis Center

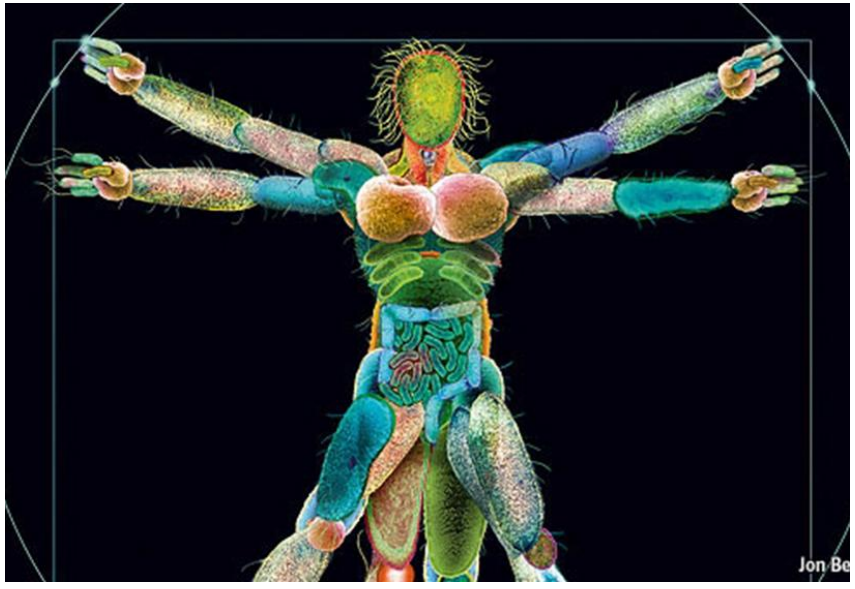
Burlington, Vermont

hashktorab@howard.edu



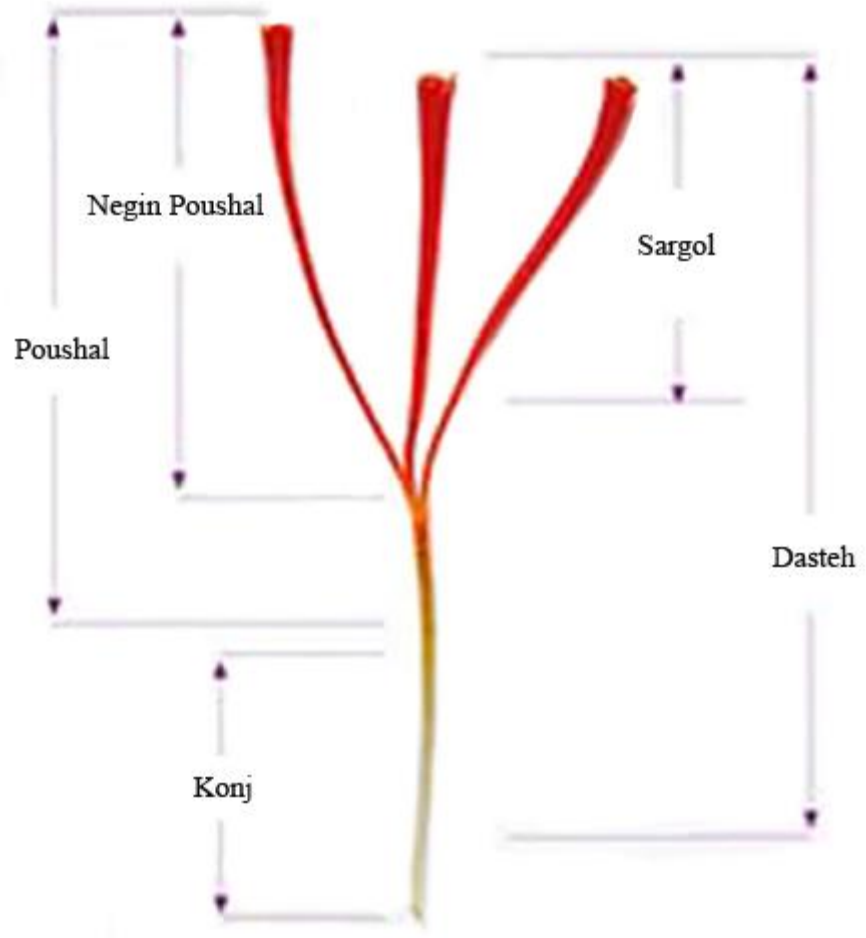
Human Genome

Human Microbiome



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



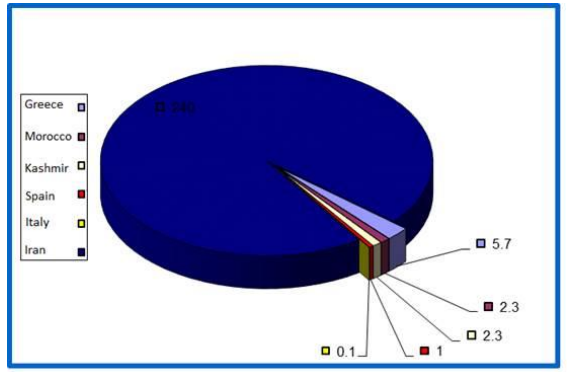
Overall color of Sargol saffron is more than others and is between 210 to 260 units.

Apart from its traditional value as a spice and coloring agent, saffron has a long history of medicinal use spanning over 2,500 years.

Moghaddasi MS. Saffron chemicals and medicine usage. J Med Plants Res. 2010;4:427–430. ; Srivastava R, Ahmed H, Dixit RK, Dharamveer, Saraf S. Crocus sativus L.: A comprehensive review. Pharmacogn Rev. 2010;4:200.

Saffron world production

How about The USA? Stay tune



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.

SAFFRON APOCAROTENOIDS: A REVIEW OF THEIR BIOMOLECULAR FEATURES AND BIOLOGICAL ACTIVITY PERSPECTIVES Laura Siracusa, Fabio Gresta, Giuseppe Ruberto (2011)

Cyrus Cylinder

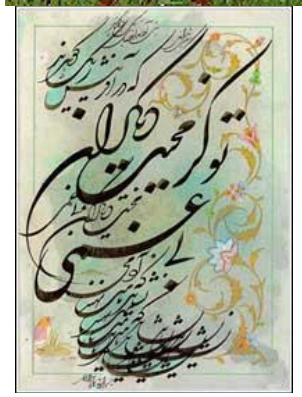
2600-year old symbol of Human Rights

Persian Empire
Professor John Lee
University of Santa Barbara

Saadi Shirazi (1200-1292)

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.



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.

Nasir Al-Mulk Mosque in Shiraz, Iran

The Nasīr al-Mulk Mosque (Persian: مسجد نصیر الملك - 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 Qājār 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 kāseh-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.

Highest 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.**

https://www.google.com/search?q=which+country+is+the+largest+producer+of+saffron+in+the+world&rlz=1C1CHBF_enUS755US755&oq=which+country+is+the+highest+producer+of+saffr&aqs=chrome.3.69i57j0l3.33912j0j7&sourceid=chrome&ie=UTF-8

Best saffron in the world

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

Please see our paper for the geography typing and quality of saffron.

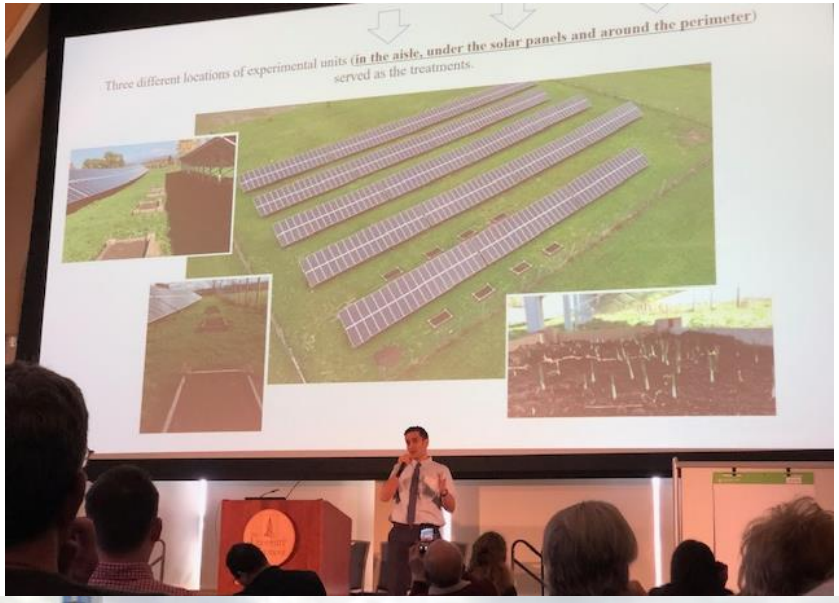
Tabtabei et al 2019. European Food Research and Technology

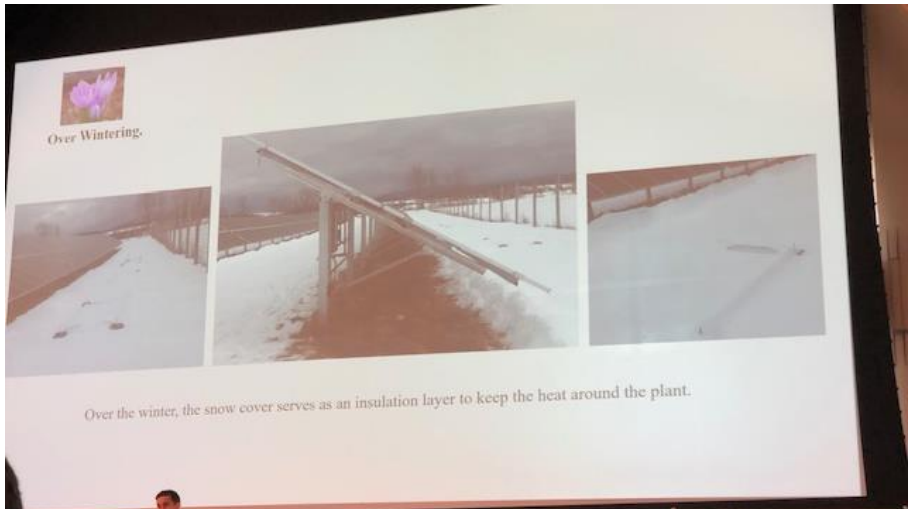
Saffron

PDO - Protected Designation of Origin

http://www.parcosirentevelino.it/Eprodotti.tipici.dettaglio.php?id=2053;ttps://www.bing.com/images/search?view=detailV2&ccid=qBk68RzP&id=276BEA4BDA9831B5D1141FD48F397FF9034EFE53&thid=OIP.qBk68RzP8gaJgk15iwRmJAHaFB&mediaurl=https%3A%2F%2Fwww.foodunfolded.com%2Fimages%2Fuploads%2Farticle-images%2Fin-article-saffron-field.jpg&exph=523&expw=771&q=saffron+production+in+iran&simid=608018217260091761&selectedindex=8&ajaxhist=0&vt=0&sim=11

Saffron in the USA
Saffron meeting in Vermont March 12, 2020





Consumption of saffron in the USA is about 46000 kg

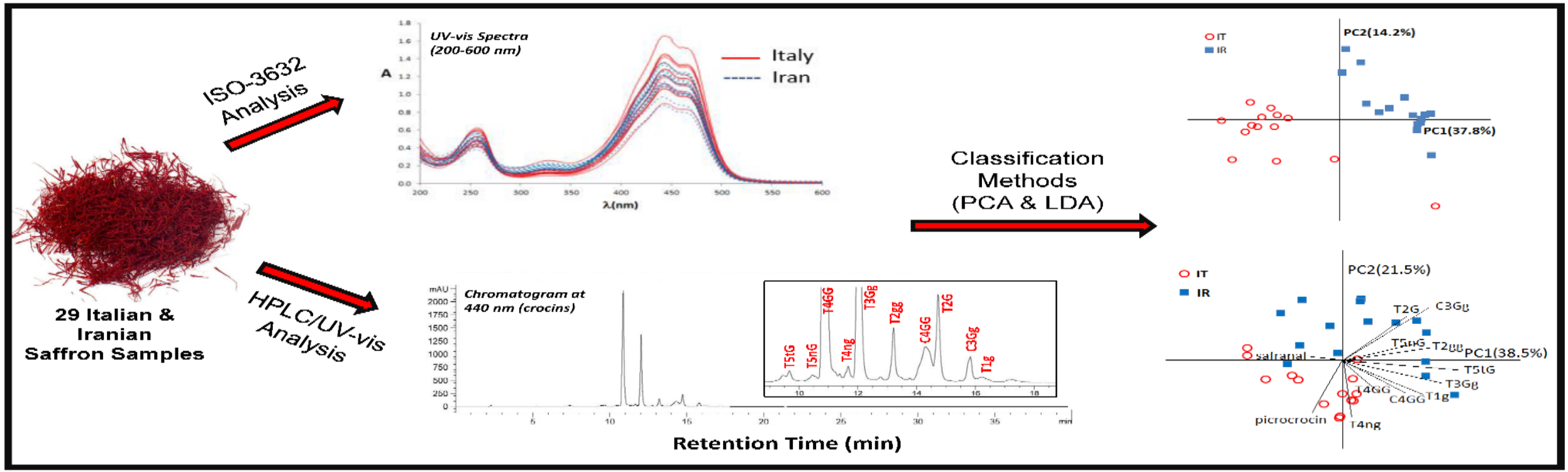
Table 1. *Saffron Nutritional value per 100 gr

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

Price:
each gram $10-50

***USDA**

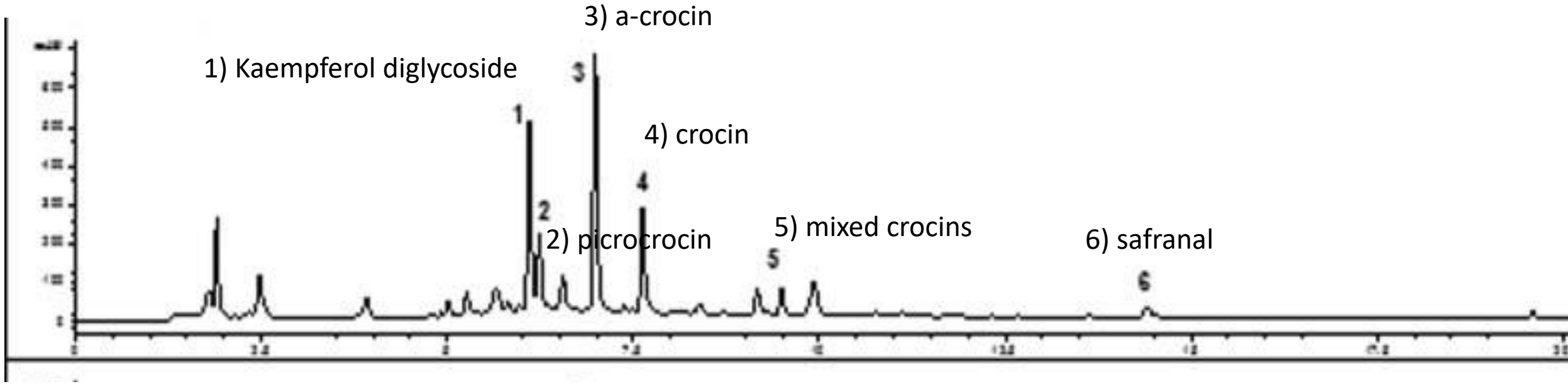
Identification saffron via HPLC and UV



ISO=International Organization For Standardization

Tabtabei et al 2019. European Food Research and Technology

Ultraviolet-visible light spectrograph and mass spectrograph data for saffron



Ultraviolet-visible light spectrograph and mass spectrograph data for saffron. From top to bottom 210 nm, 280 m, and mass spectrography Total Ion Content profiles for saffron. Peaks associated with major constituents are numbered as follows: 1) Kaempferol diglycoside, 2) picrocrocin, 3) a-crocin, 4) crocin, 5) mixed crocins 6) safranal.

Comparison of Saffron from different part of the world

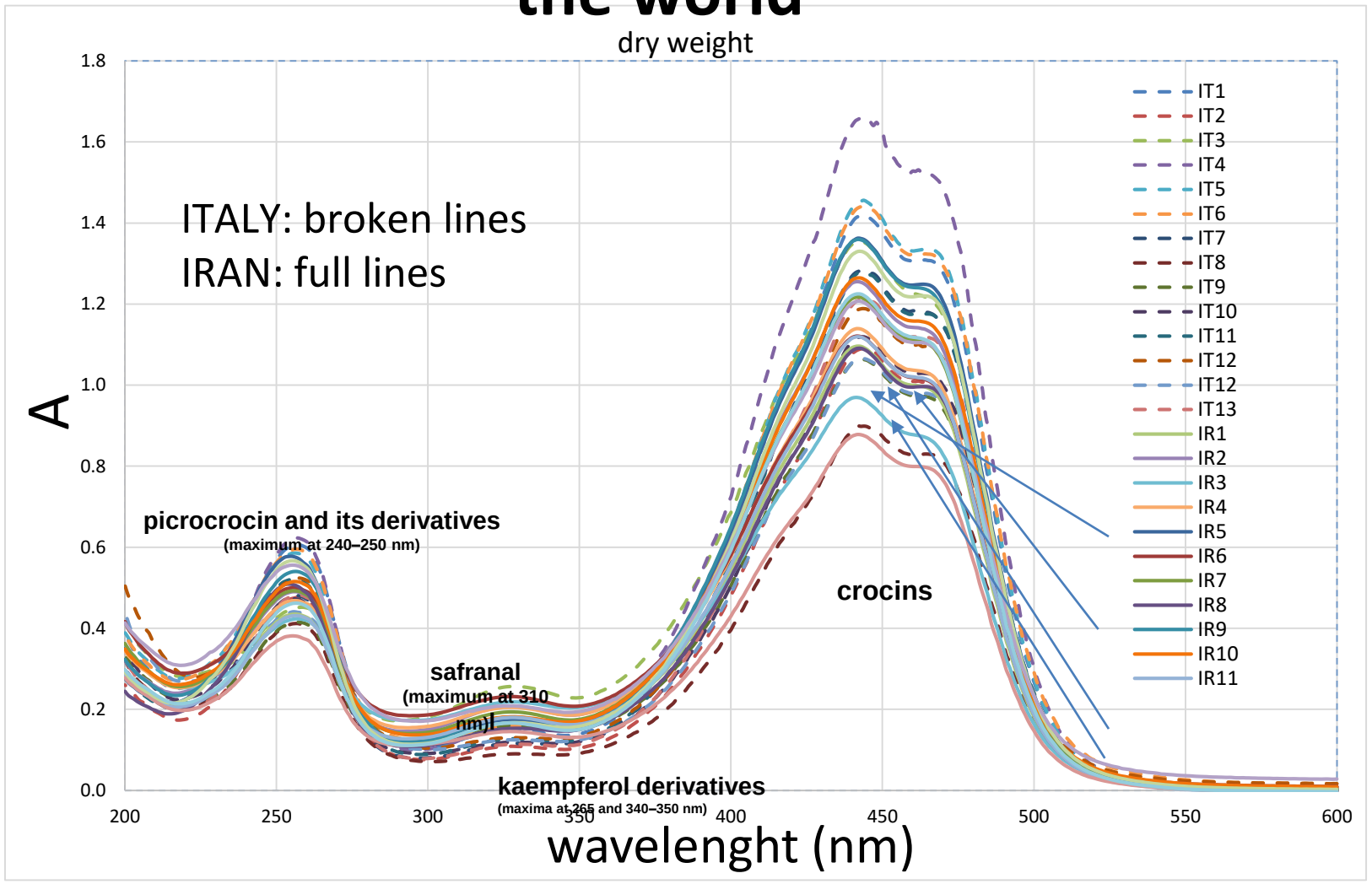


Fig. UV–Vis spectra of Italian and Iranian saffron samples. a Raw UV–Vis spectra of all Iranian and Italian samples; (b) UV–Vis spectra of all Iranian and Italian samples after multiplicative scatter correction (MSC) treatment; (c) first-order derivative spectra of all samples

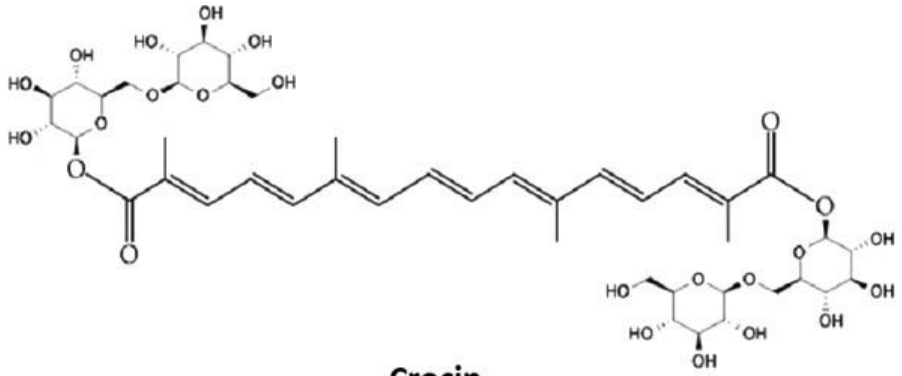
Tabtabei et al 2019. European Food Research and Technology

Table 2. Saffron Constituents and their responsibilities

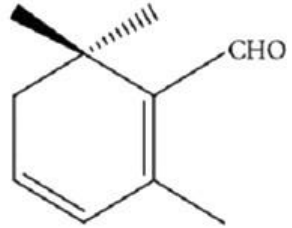
Constituent	Responsible	Action
Crocin	color	Anti-Inflammation/Anti- ROS
Picrocrocin	bitter taste	Anti-Inflammation/Anti- ROS
Safranal	Aroma	Anti-Inflammation/Anti- ROS

Saffron contains over 150 potentially biologically active agents, including a range of carotenoids (Bathaie and Mousavi,2010).

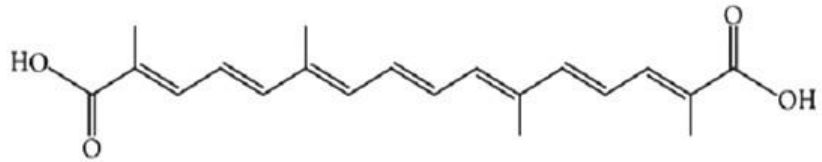
Ashktorab et al., Nutrients, 11 (5) 2019 Apr 26



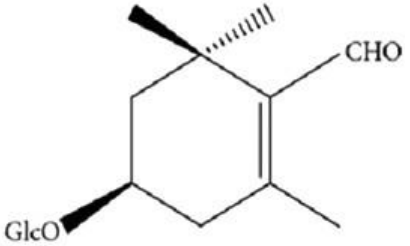
Crocin



Safranal



Crocetin



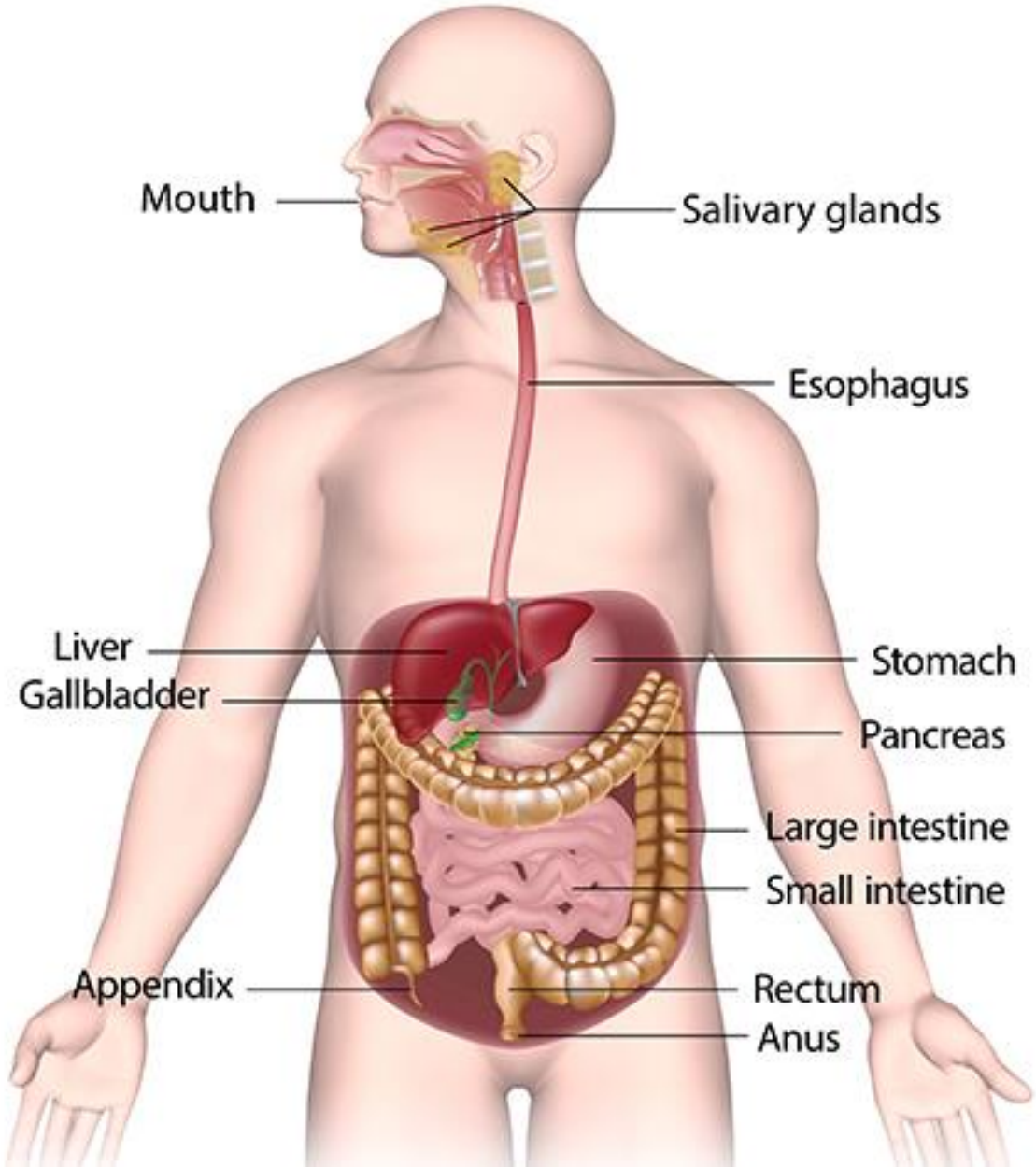
Picrocrocin

Chemical structures of main secondary metabolites of saffron.

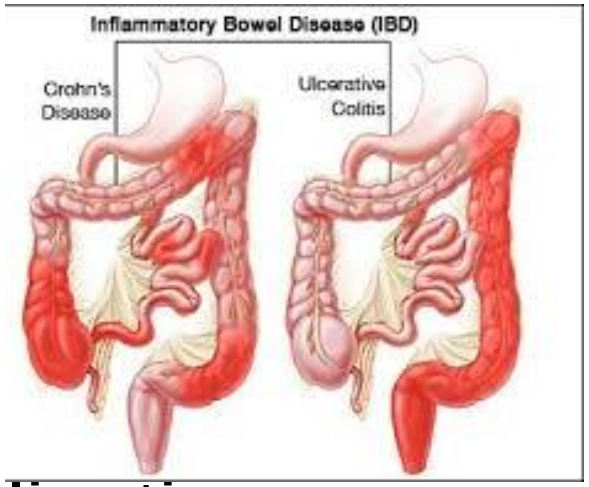
Mojtaba Shafiee et al; *J. Agric. Food Chem.* **2017,** 65, 10837-10843. DOI: 10.1021/acs.jafc.7b03762

Gastrointestinal (GI) diseases in the US

The Digestive System



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



- In 2015,
  - An estimated 3 million hospitalizations,
  - 54.4 million ambulatory care visits,
  - 144300 deaths.

- Spending on GI diseases
  - An estimated at $135.9 billion per year.

Anne F Peery et al. Gastroenterology, 156 (1), 254-272.e11 Jan 2019;
Everhart JE1, Ruhl CE. Gastroenterology. 2009 Apr;136(4):1134-44.

Burden of Colorectal Cancer (CRC)

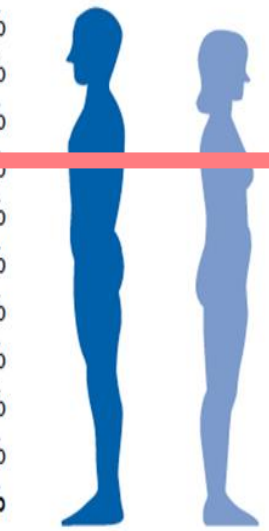
- World-wide about 1,400,000 people are diagnosed with colorectal cancer each year
- 2.4 million cases of CRC diagnosed every year by 2035.
- Both women and men
- All races
- Second leading cause of cancer death in US
- American Cancer Society estimates in 2020
  - 97,220 new cases
  - 50,000 deaths
  - About 27,400 patients will have had their cancer metstasiz.*

*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.

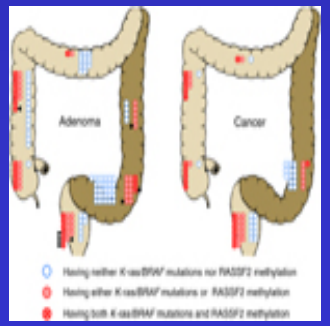
Estimated Deaths

Male			Female		
Lung & bronchus	83,550	26%	Lung & bronchus	70,500	25%
Prostate	29,430	9%	Breast	40,920	14%
Colon & rectum	27,390	8%	Colon & rectum	23,240	8%
Pancreas	25,020	7%	Pancreas	21,310	7%
Liver & intrahepatic bile duct	20,540	6%	Ovary	14,070	5%
Leukemia	14,270	4%	Uterine corpus	11,350	4%
Esophagus	12,850	4%	Leukemia	10,100	4%
Urinary bladder	12,520	4%	Liver & intrahepatic bile duct	9,660	3%
Non-Hodgkin lymphoma	11,510	4%	Non-Hodgkin lymphoma	8,400	3%
Kidney & renal pelvis	10,010	3%	Brain & other nervous system	7,340	3%
All sites	**323,630**	**100%**	**All sites**	**286,010**	**100%**



Estimates are rounded to the nearest 10, and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder. Ranking is based on modeled projections and may differ from the most recent observed data.

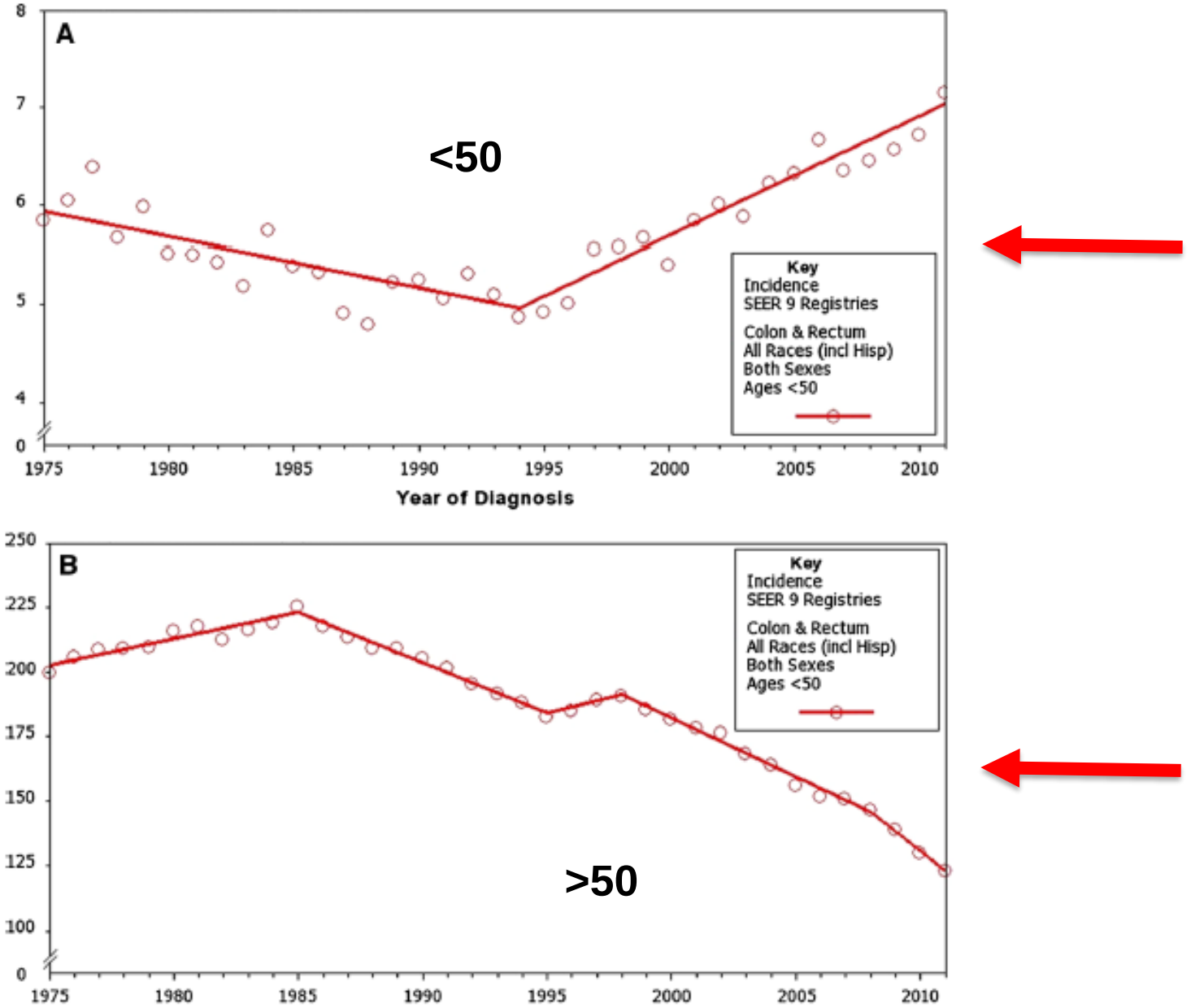
©2018, American Cancer Society, Inc., Surveillance Research



American Cancer Society, Cancer Facts and Figures 2018

Siegel et al, CA Cancer J Clin 2014; 64:104-117

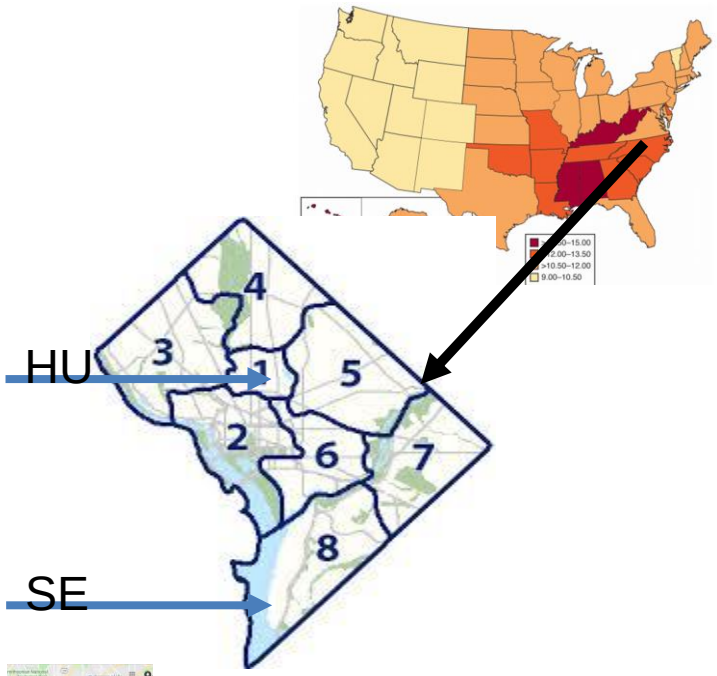
Colorectal Cancer in Young Adults



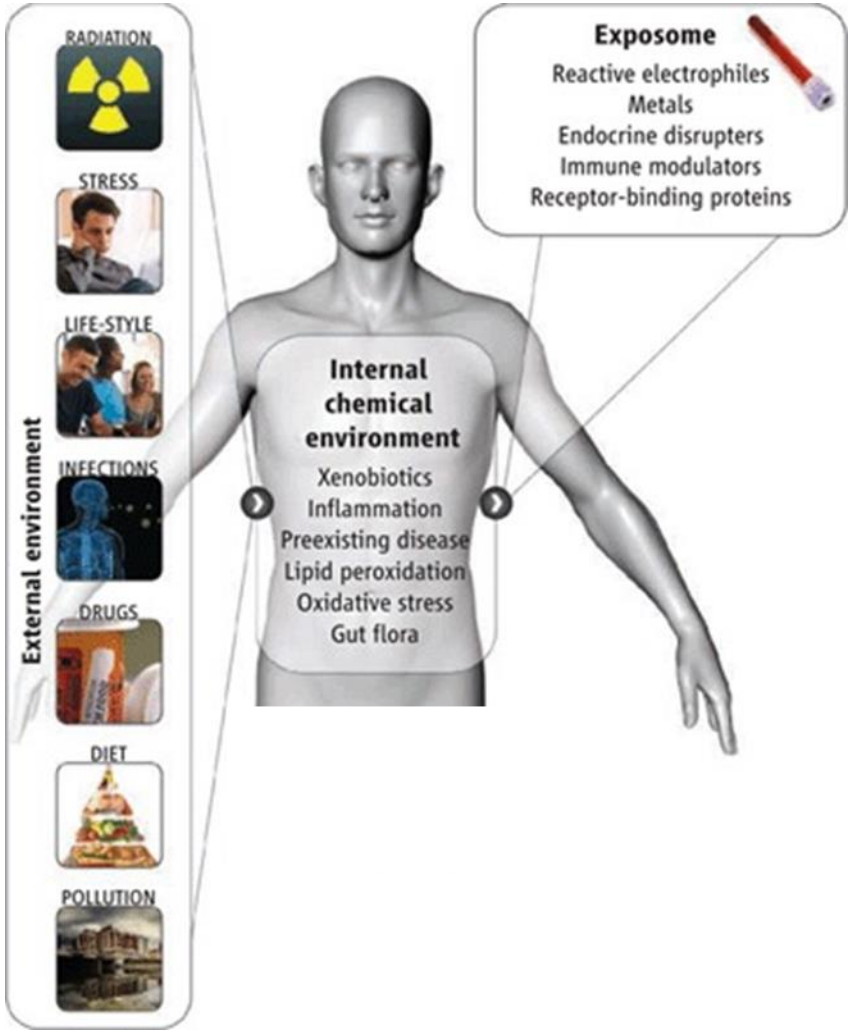
Dig. Dis Sci 2015, 60:722

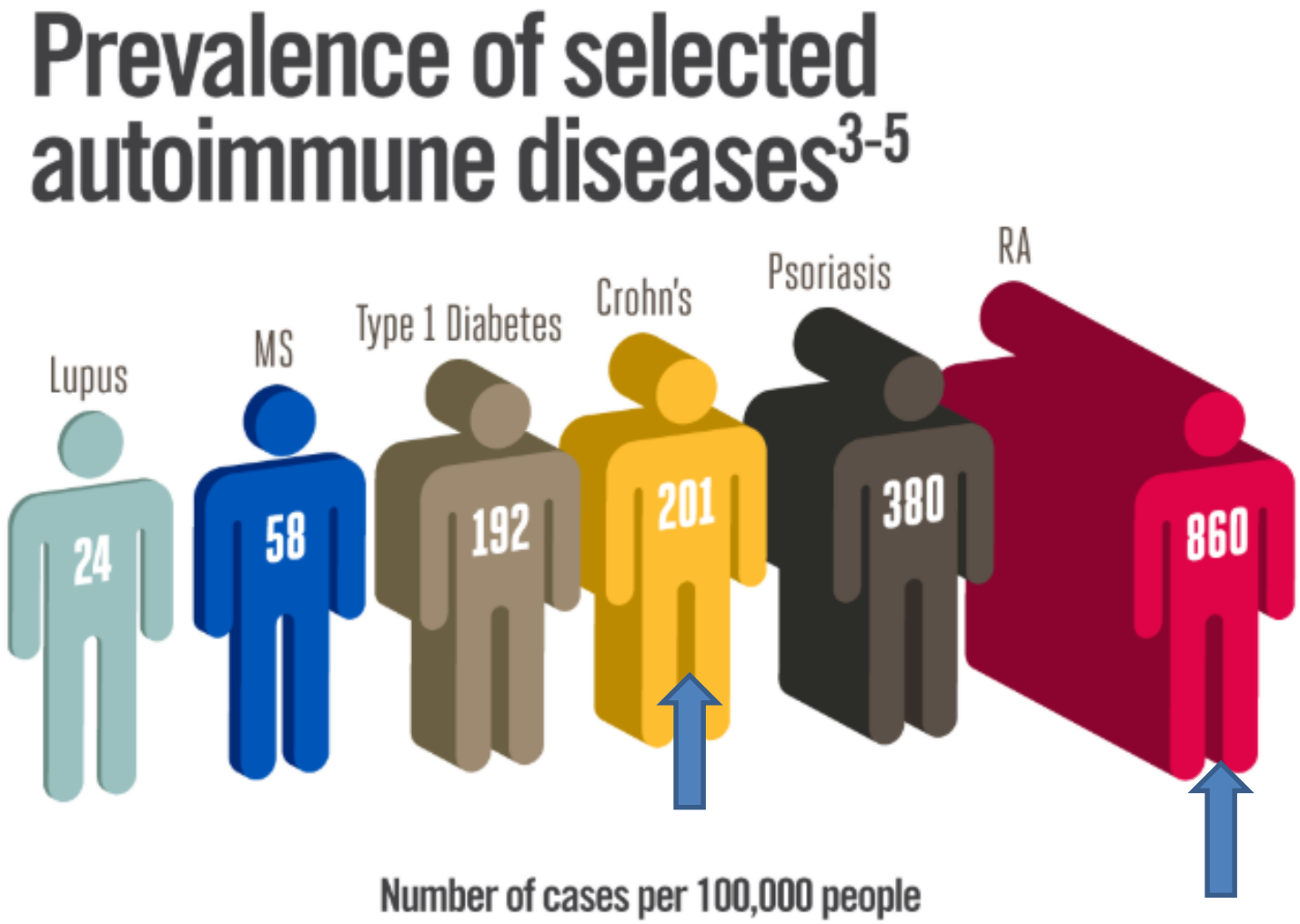
Time trend of CRC incidence in USA. Modified from the NCI web site. A) Age <50, B) age >50. Ashktorab et al 2016, Dig Dis Sci. 2016 Oct;61(10):3026-30. doi: 10.1007/s10620-016-4207-1.

Environmental exposures (E-Score) and Genetics (G-score)



Washington DC has the different life expectancy based on wards





Arthritis is a common health problem in the US population, affecting more than 46 million people and resulting in disability for 19 million people. In fact, among chronic **diseases in the US, arthritis causes more disability than any other condition**, including heart disease, diabetes, and back or spine problems. RA is the third most common type of arthritis behind osteoarthritis (prevalence 26.9 million) and gout (prevalence 6.1 million). RA affects approximately **1.3 million in the US.**

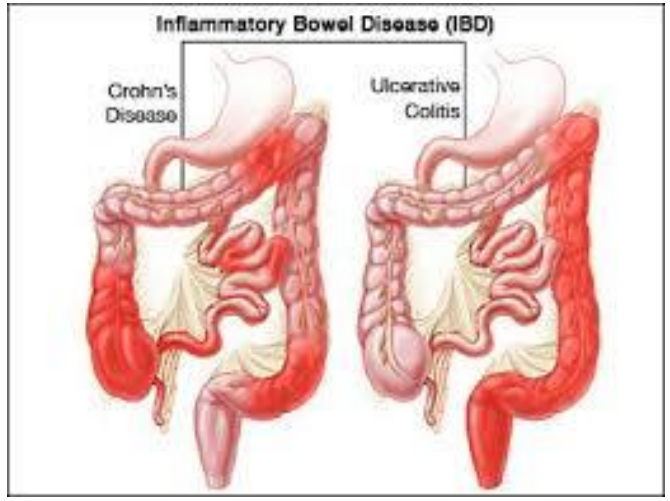
https://rheumatoidarthritis.net/what-is-ra/ra-statistics/

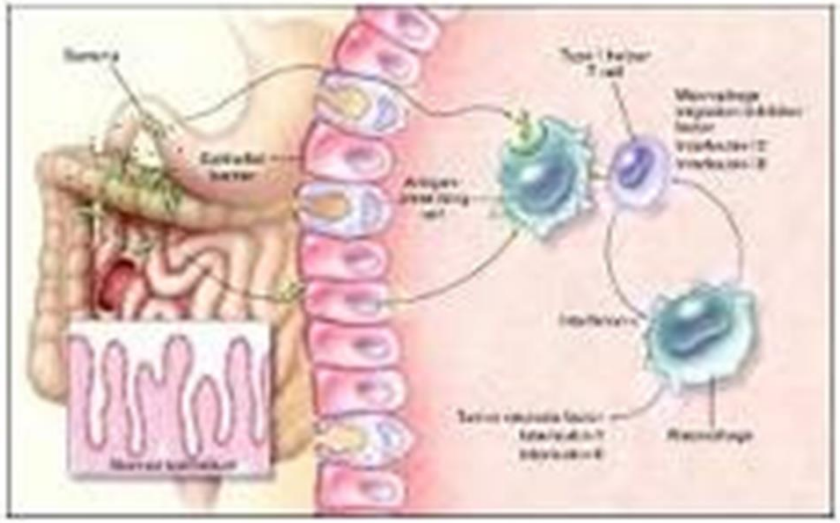
Inflammatory Bowel Disease

- **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.**





Scope of IBD in USA

Estimated prevalence[1]

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

Physician visits: >700,000/year[2]

Hospitalizations: 100,000/year[2]

Annual direct costs: ~$4 billion[3]

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]

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.

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

Saffron and protection against diseases

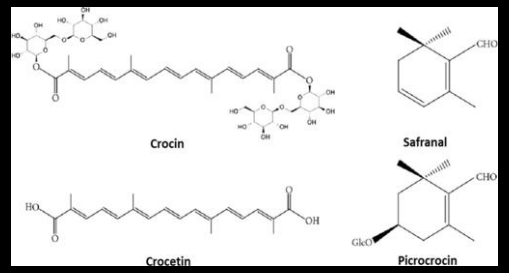
Microbiome and colon disease

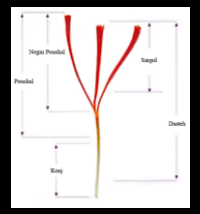
GUT Brain axis

GUT and Joint axis

GUT and body axis

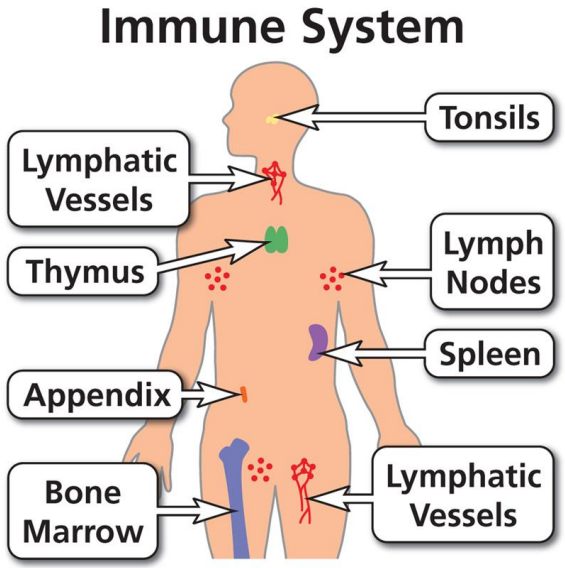
Microbiome and Organes

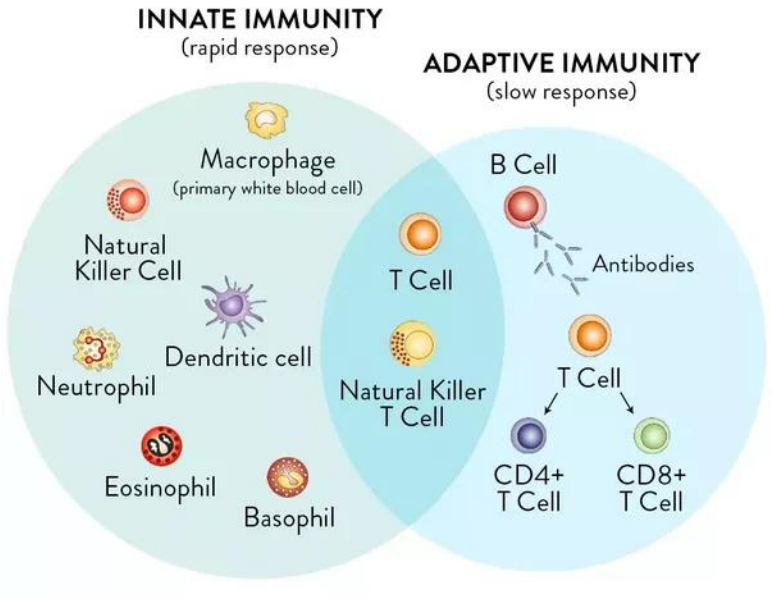




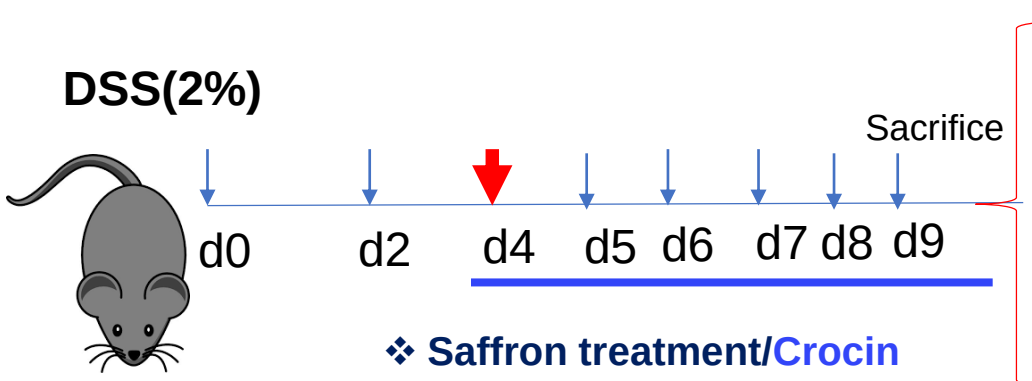
Saffron effect on colitis via anti inflammatory and anti oxidant pathway

- An immune system is a host defense system comprising many biological structures and processes within an organism that protects against disease. To function properly, an immune system must detect a wide variety of agents, known as pathogens, from viruses to parasitic worms, and distinguish them from the organism's own healthy tissue.
- In many species, there are two major subsystems of the immune system: the innate immune system and the adaptive immune system. Both subsystems use humoral immunity and cell-mediated immunity to perform their functions. In humans, the blood–brain barrier, blood–cerebrospinal fluid barrier, and similar fluid–brain barriers separate the peripheral immune system from the neuroimmune system, which protects the brain.





Experimental setup



❖ **Saffron treatment/Crocin treatment/Vehicle control**

7 weeks old
Male mice
(C57BL/6)

Concentrations of Saffron aqueous extract (SFE)

❖ **5-25mg**

Samples Analyzed for

Anti inflammatory makers

Pro inflammatory markers

mononuclear leukocyte (MNL)

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

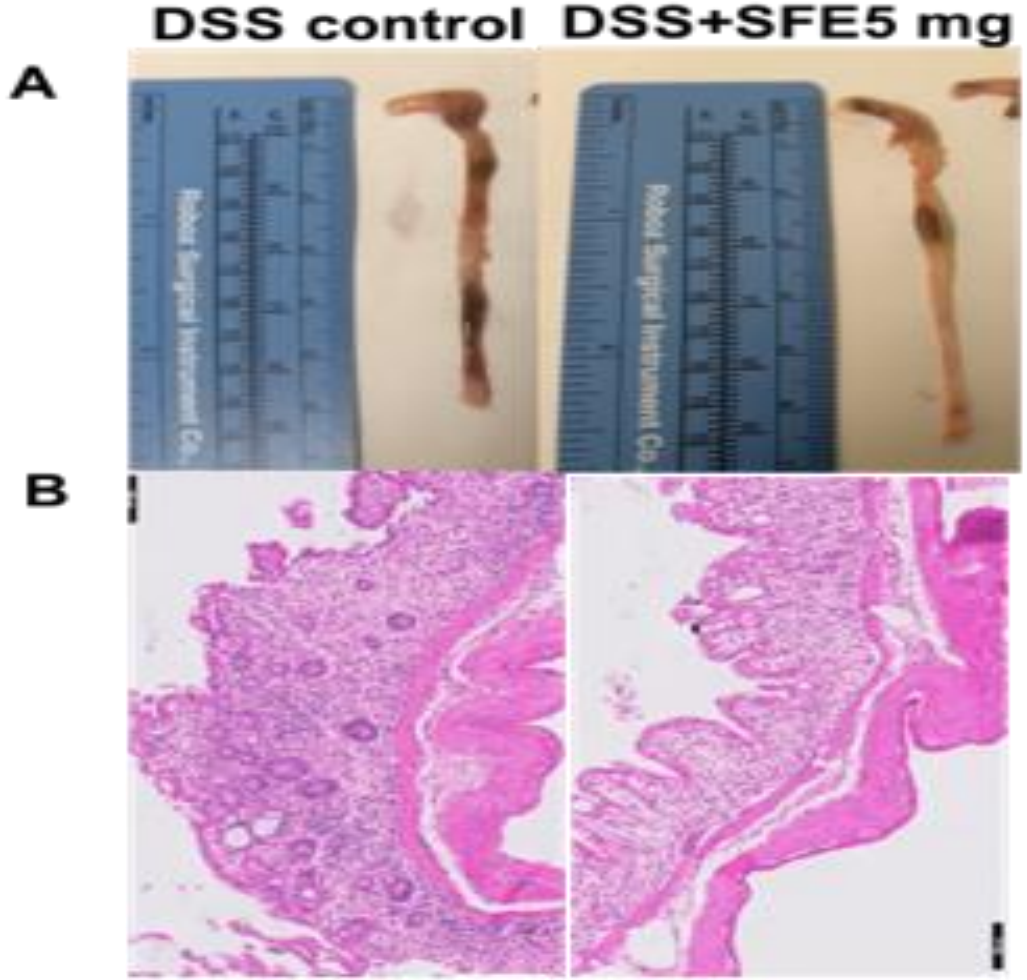
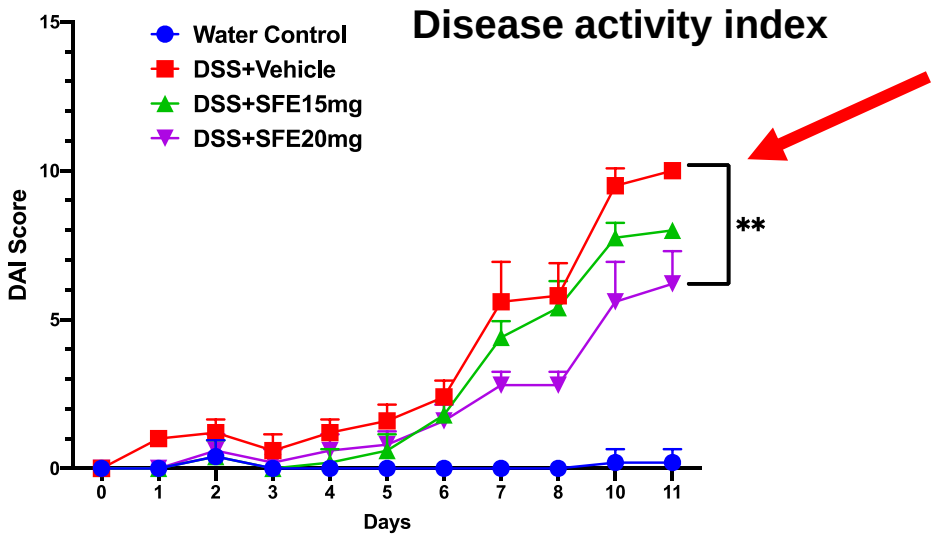
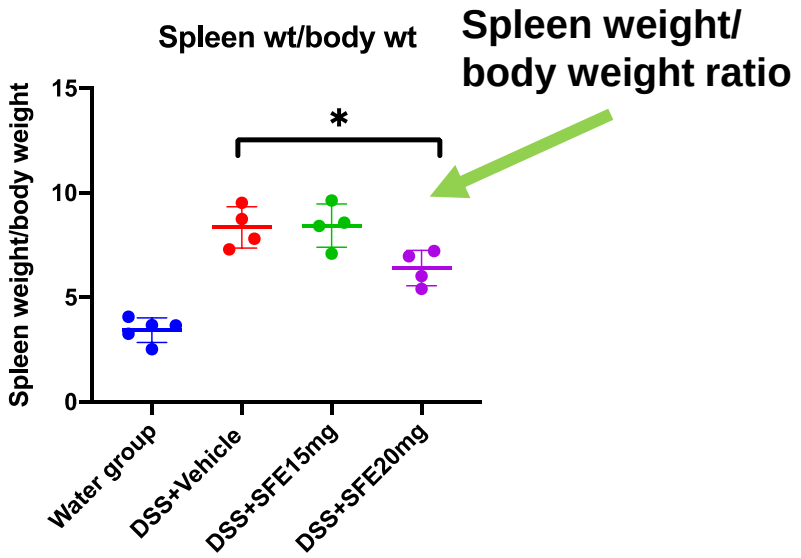


Figure 1: Colon Length and Histology of colon tissue

Saffron Increases *Disease activity index and Spleen weight



Paired t test b/w DSS Vehicle and DSS+SFE20mg
Representation of one experiment (fourth set)



Paired t test b/w DSS Vehicle and DSS+SFE20mg
Representation of one experiment (fourth set)

- **There was significant <u>decrease</u> in DAI score with 20mg Saffron concentration**
- **Spleen to body weight ratio** <u>increased</u>

*The DAI score was calculated as the sum of the weight loss score, the diarrheal score and the hematochezia score

Saffron

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

- **Different pathways and exert its effect as anti-inflammatory, anti-ROS, and anti-proliferative**

Ashktorab et al., Nutrients, 11 (5) 2019 Apr 26

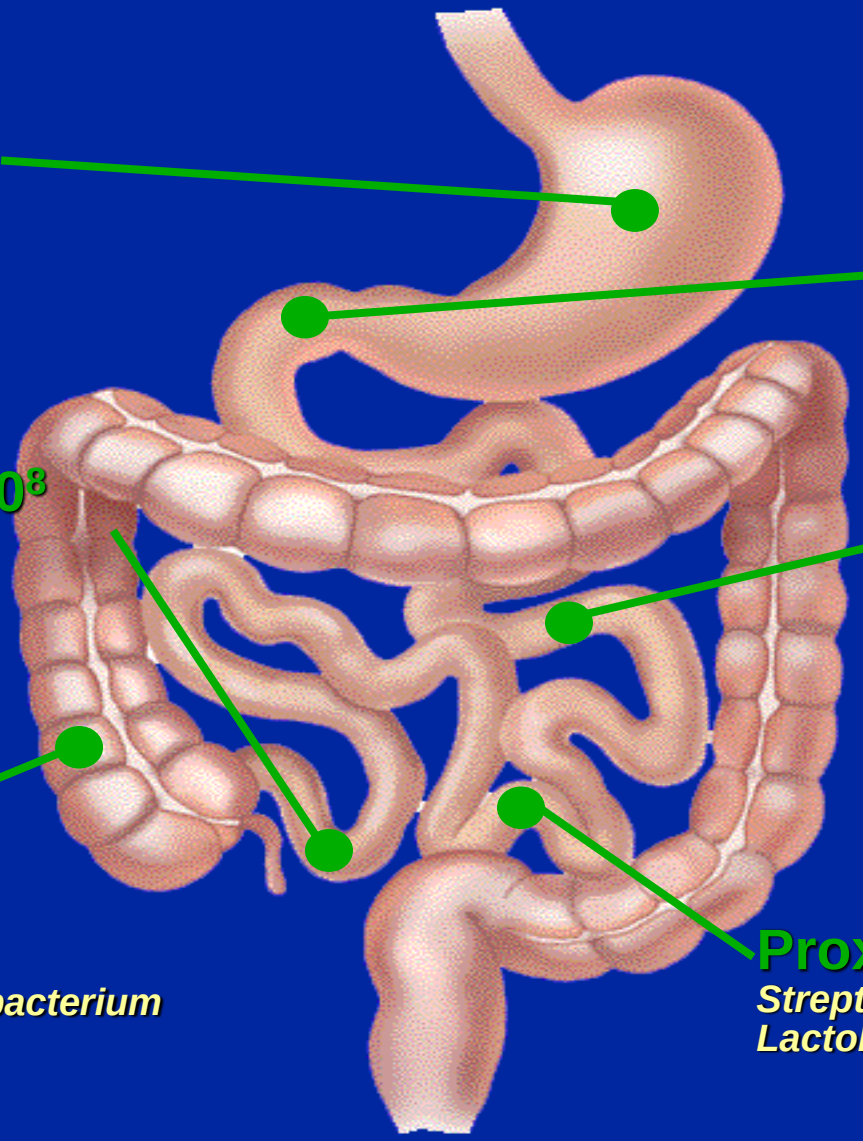
Khorasany AR, Hosseinzadeh H.., J Basic Med Sci. 2016;19: 455-469.

- **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

Science 2019 Feb 22, vol363, page 833

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

Efficacy and Safety of Saffron Supplementation: Current Clinical Findings

Given the role of oxidative stress and anti inflammatory in many diseases, considerable interest has been shown into the potential role of saffron supplementation as a treatment for a range of diseases.

BROADHEAD et al., Critical Reviews in Food Science and Nutrition, 56:2767–2776, (2016)

Cognition

Alzheimer's disease, which is believed to involve immune-mediated oxidative damage to CNS tissue, resulting in decreased cognitive function. There is some evidence that saffron extracts may inhibit beta-amyloid aggregation in animal models, a key step in the pathogenesis of Alzheimer's disease (Papandreou et al., 2006).

Based on such findings, two small clinical studies have been conducted to assess the efficacy of saffron in Alzheimer's Disease. Compared to placebo, 30 mg saffron supplementation daily for 16 weeks resulted in improved cognitive function (change in both Alzheimer's Disease Scale-cognitive subscale and Clinical dementia ratings-scale sums of boxes significant, $p < 0.0001$ for both) (Akhondzadeh et al., 2010a).

Crocetin has also been trialled as a therapy for sleep complaints, although the crocetin for this study was sourced from Gardenia jasminoides, not saffron. In a double-blind, placebo-controlled trial of 21 males with mild sleep complaints, crocetin improved both objective (actigraph) and subjective measures of sleep quality ($p=0.025$ for reduction in waking episodes compared to placebo) (Kuratsune et al., 2010). The success of using crocetin from non-saffron sources suggests that these may offer cheaper alternative means of sourcing some saffron-based compounds for future therapeutic use.

Mood

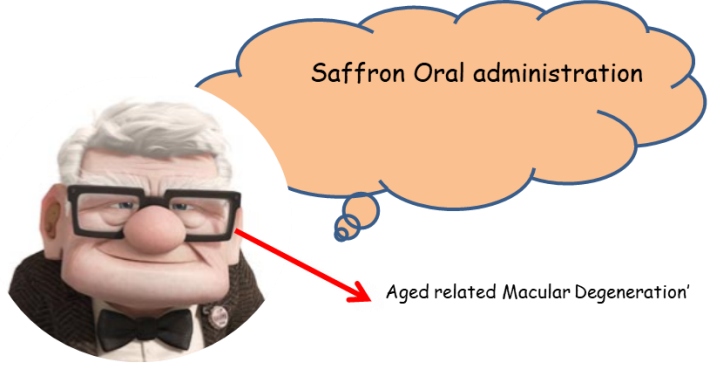
Two small, 6-week trials have compared 30 mg/daily saffron to placebo for the treatment of mild-moderate depression, with significant improvements in the Hamilton depression scale noted with saffron therapy (Akhondzadeh et al., 2005; Moshiri et al., 2006).

These have been followed by two other trials comparing saffron to currently used antidepressants. One 6-week study compared the same dose of saffron to imipramine (100 mg/daily) and another 9-week trial compared 30 mg/daily saffron to 10 mg/daily fluoxetine. Both trials demonstrated non-inferiority of saffron in treating mild-moderate depression as measured by the Hamilton depression scale (Akhondzadeh Basti et al., 2007; Akhondzadeh et al., 2004).

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

Questionnaire	Weeks into treatment	Treatment Group					
		saffron			Fluoxetine		
		Mean	SD	*p-value**	Mean	SD	*p-value**
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

Aged Macular degeneration (AMD)



In MEN

Promising results have also been observed in small clinical studies in humans. The most common degenerative retinal condition worldwide is AMD, a disease that is thought to involve immune-mediated oxidative damage to retinal tissue.

Saffron supplementation has been shown to delay improve focal electroretinogram (fERG) findings in one small placebo-controlled study of patients with AMD (change in fERG amplitude 0.25 log uV vs. ¡0.003 log uV, p < 0.01) (Falsini et al., 2010). Longer-term follow-up of these patients demonstrated ongoing saffron supplementation improved visual acuity and fERG parameters, potentially delaying disease progression (Piccardi et al., 2012, 2019).

Piccardi et al. Antioxidant Saffron and Central Retinal Function in ABCA4-Related Stargardt Macular Dystrophy. Nutrients. 2019 Oct 15;11(10):2461.

BROADHEAD et al., Critical Reviews in Food Science and Nutrition, 56:2767–2776, (2016)

Sexual Dysfunction and Infertility (n = 4 studies)

Modabbernia et al. (2012) found that saffron supplementation (30 mg/d for 4 weeks) was efficacious in treating fluoxetine-related erectile dysfunction.

Modabbernia A, Sohrabi H, Nasehi AA, Raisi F, Saroukhani S, Jamshidi A, et al. Effect of saffron on fluoxetine-induced sexual impairment in men: randomized double-blind placebo-controlled trial. Psychopharmacology (Berl) 2012;223:381–8.

Reproductive disease

In women with symptoms of PMS, supplementation with 30 mg/day saffron for two menstrual cycles resulted in improvement of symptoms as measured by Daily Symptoms Report and Hamilton Depression Rating Scale compared to placebo (difference between two groups on both measures significant, df D 48, p < 0.001 for both) (Agha-Hosseini et al., 2008).

Two small, 4-week, placebo-controlled trials of saffron as a treatment for fluoxetine-induced sexual dysfunction in men and women showed that it was of benefit in reducing overall sexual dysfunction in both genders. Men experienced greater erectile function and intercourse satisfaction, whilst women achieved greater arousal and reduced pain with saffron supplements (Kashani et al., 2013; Modabbernia et al., 2012).

Saffron can be effective in metabolic syndrome

Saffron and its active components including crocin, crocetin, and safranal are potential therapeutic candidates for attenuating:

metabolic syndrome (MetS).

MetS complications including hypertension, hyperglycemia, obesity, and dyslipidemia.

Razavi et al., J Sci Food Agric. 2017;97(6):1679–1685. doi:10.1002/jsfa.8134; Mojtaba Shafiee et al; *J. Agric. Food Chem.* **2017,** 65, 10837-10843. DOI: 10.1021/acs.jafc.7b03762
;

Cardiovascular

A single, short duration trial has investigated saffron in lipid metabolism and arterial disease.

Oral consumption of 50 mg saffron dissolved in 100 mL milk daily for 6 weeks was undertaken in 10 healthy participants and to 10 patients with coronary artery disease, and these results were compared to 10 control patients consuming milk only. Both intervention groups experienced a significant reduction in lipoprotein oxidation susceptibility (reduction from 66.4 to 38.3 units in healthy participants, from 76.0 to 48.8 in patients with CAD, $p < 0.001$ for both), whereas the control patients did not

(Verma and Bordia, 1998).

BROADHEAD et al., Critical Reviews in Food Science and Nutrition, 56:2767–2776, (2016)

saffron supplementation significantly reduced depression symptoms compared to placebo

A recent study, by Shahmansouri et al. 2014, not included in the 2013 meta-analysis by Hausenblas et al 2015, examined the effects of saffron supplementation versus fluoxetine in patients with major depressive disorder who had undergone percutaneous coronary intervention.
The researchers found that short-term therapy of six weeks with saffron supplementation produced similar improvements in symptoms of depression as the antidepressant medication fluoxetine.

Lopresiti and Drummond found a minimal frequency of adverse events. An inspection of frequency data indicates increased reports of sedation/drowsiness, headache, dry mouth, constipation and sexual dysfunction with antidepressant treatment compared with saffron.

Depression (n = 6 studies) n = 2 placebo controlled trials, n = 4 antidepressant controlled trials).

Lopresti AL, Drummond PD. Saffron (Crocus sativus) for depression: a systematic review of clinical studies and examination of underlying antidepressant mechanisms of action. *Hum Psychopharmacol*. 2014;29(6):517–527. doi:10.1002/hup.2434

Toxicity

The safety of any potential supplementation therapy needs carefully evaluation to ensure that the potential adverse effects of therapy are well understood. Although saffron has been used as a foodstuff without complication for many centuries, much of the reported toxicity data for saffron is anecdotal at best.

Doses up to 1.5 g/daily are considered relatively safe, and harmful effects are reportedly encountered with doses >5 g/day, with doses of 20 g/daily considered a lethal dose (Schmidt et al., 2007).

BROADHEAD et al., Critical Reviews in Food Science and Nutrition, 56:2767–2776, (2016)

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 Antioxidant Property and Anti-inflammatory effect	Down-regulation of hTERT gene Down-regulation of the expression of catalytic subunit of enzyme telomerase Increased the levels of GST, SOD and CAT Reduced myeloperoxidase activity, malondialdehyde Inhibition of COX 2, iNOS, NF-kB	43, 44, 47
Pancreatic Cancer	crocetin	Cell cycle arrest at G2/M Phase	Reduced expression of Cdc-2 (hyperphosphoryltion) 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

Schematic representation of saffron-mediated protective responses in MetS pathology

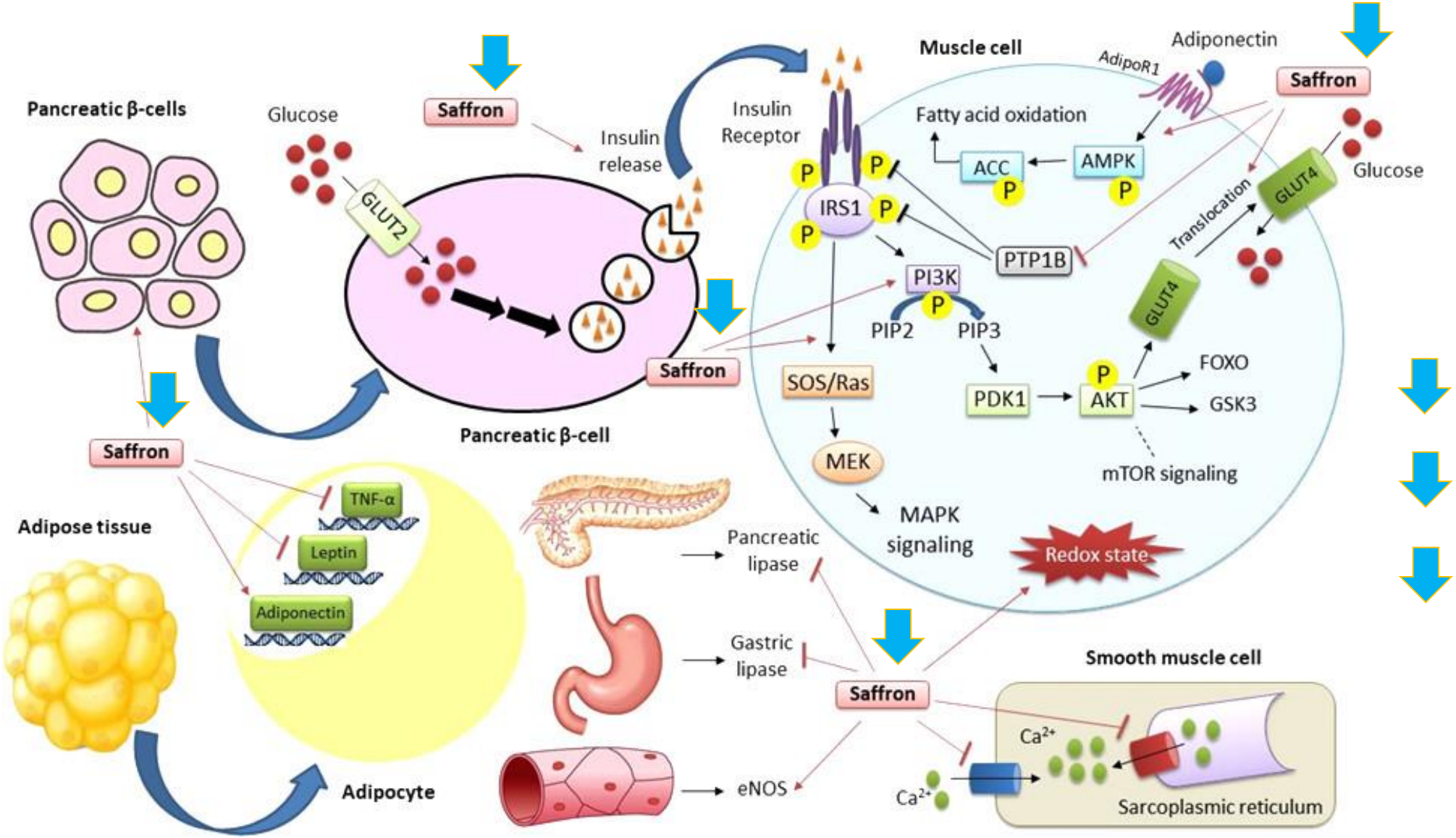


Figure. Saffron attenuates MetS complications including hypertension, hyperglycemia, obesity, and dyslipidemia.

Mojtaba Shafiee et al; *J. Agric. Food Chem.* **2017,** 65, 10837-10843. DOI: 10.1021/acs.jafc.7b03762

Saffron

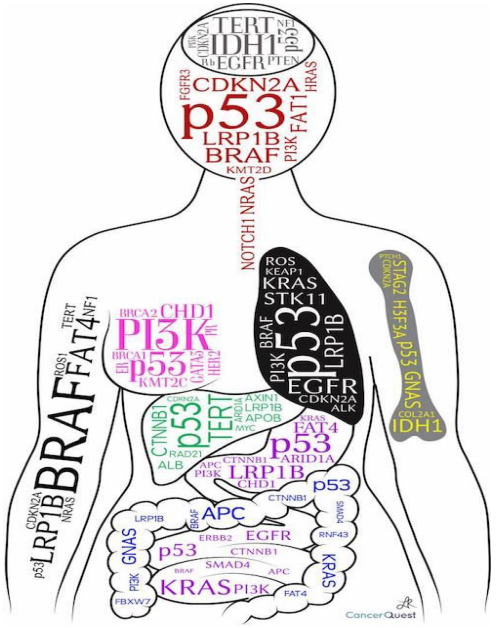
GUT-body axis (brain, joint, eye,..)

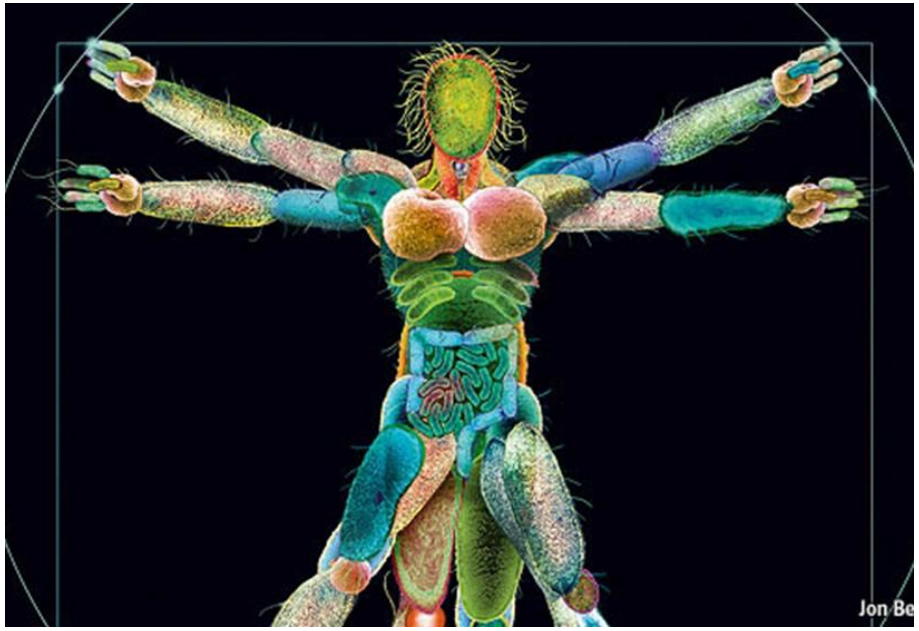
-anti-inflammation
-dysbiosis
-anti-toxigenic bacteria
-Anti-ROS
-interventional on moderate mood disorder

Summary

- **Saffron with induce anti-ROS factors,**
  - **thru Nrf2-HO1.**
- **Saffron has ability to alter the macrophage population during the intestinal inflammation in mouse model of colitis by:**
- **Increasing the anti-inflammatory signature**
- **Decrease Proinflammatory immune signature**

Saffron effect on immune signature and Microbiome





Precision medicine using Genome and Microbiota

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