

# Flavonoids and Inflammation

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# Phytonutrient Classes

- Carotenoids
- Flavonoids (Polyphenols) including Isoflavones (Phytoestrogens)
- Inositol Phosphates (Phytates)
- Lignans (Phytoestrogens)
- Isothiocyanates and Indoles
- Phenols and Cyclic Compounds
- Saponins
- Sulfides and Thiols
- Terpenes



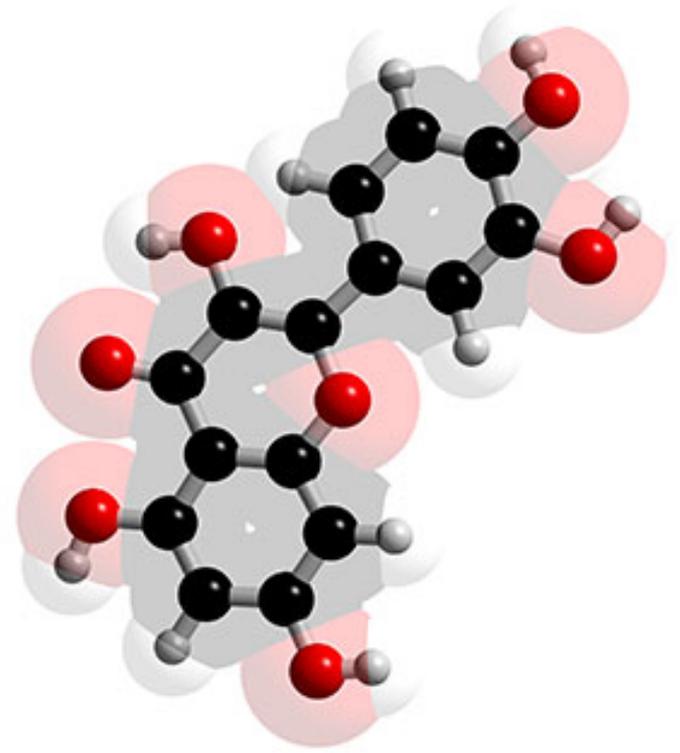
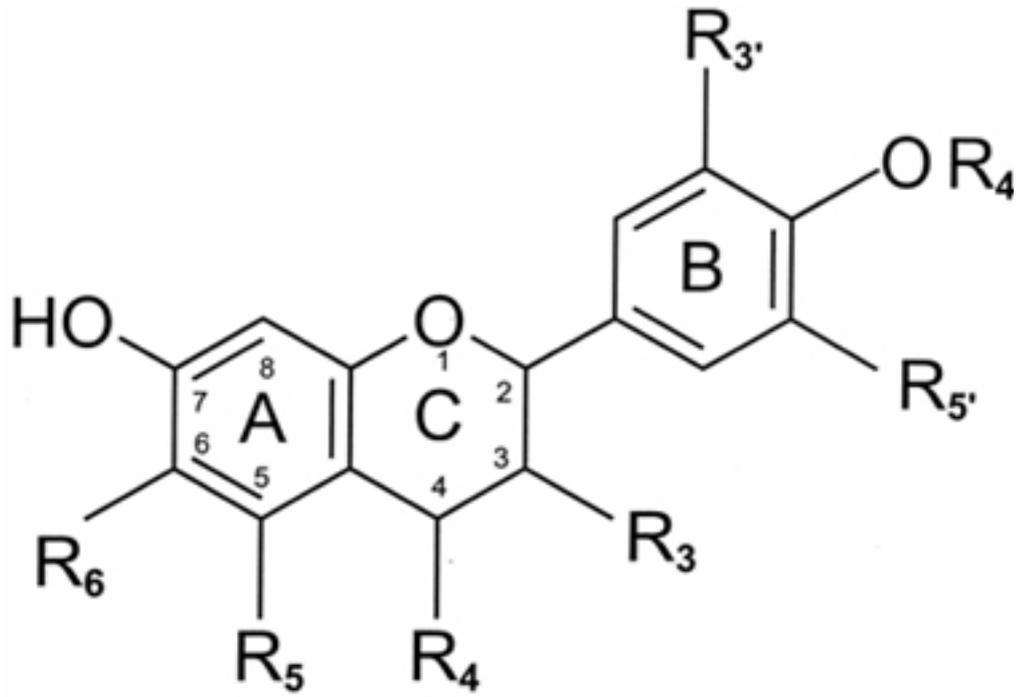
**150,000 to 200,000 Edible Plant Species on Earth and we eat only 150 to 200 Species There are estimates of the number of phytochemicals as 100,000 to 1 million. New phytochemicals are being discovered constantly.**

# Flavonoids and Larger Polyphenols

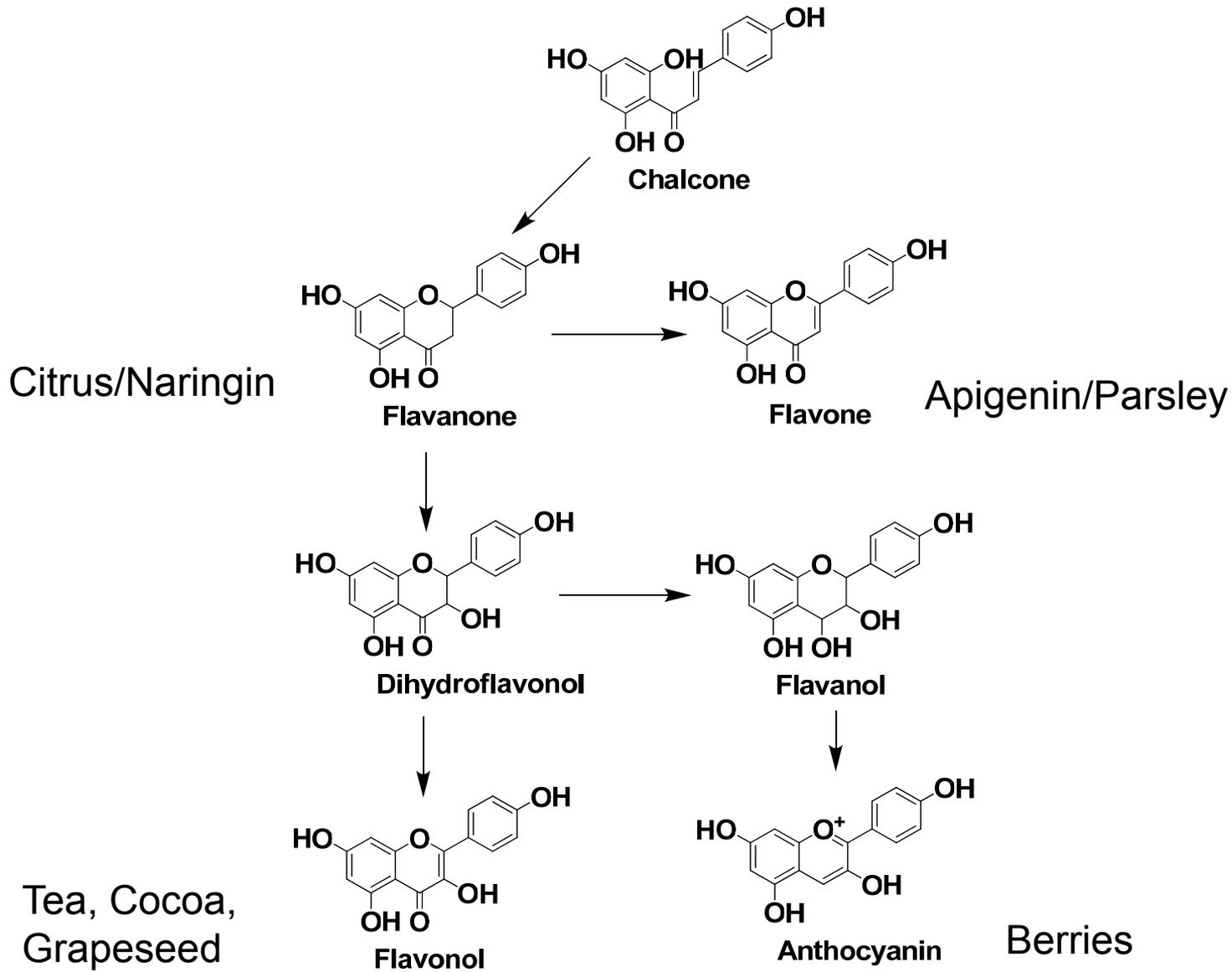
- **Flavonoids are widely accepted to be the predominant polyphenols in our diet and typically average approx 300 MW and include anthocyanins, flavonols (quercetin), isoflavones, flavanols (catechins), etc.**
- **However larger polyphenolic compounds (>1000 MW) are also ubiquitous in our diet and their amounts in our diets have been underestimated, in part due to the lack of authentic chemical standards, etc. These compounds include tannins which are divided into two groups :1) proanthocyanidins or condensed tannins: found in green tea, cacao/chocolate, blueberries, cranberries, grape seed, etc.; and 2) hydrolyzable tannins (ellagitannins and gallotannins) found in pomegranate, strawberries, raspberries (red and black), some nuts (peels of walnuts, almonds, pecans) and oak-aged beverages, etc.**
- **Condensed tannins from cocoa are commonly grouped with the flavonoids since they contain catechin units but by strict chemical definition condensed tannins are not flavonoids.**

# Flavonoids and Inflammation

- **More than 6,000 varieties of flavonoids have been identified and they are consumed in the largest amounts of total phytochemicals in the diet (ca. 500 to 2000 mg/day) from multiple sources.**
- **Flavonoids have a molecular wt of about 300 Daltons and are called bioflavonoids as they contribute significantly to antioxidant activity of the human diet.**
- **Flavonoids are able to inhibit mediators of the inflammatory process such as NF-kB.**



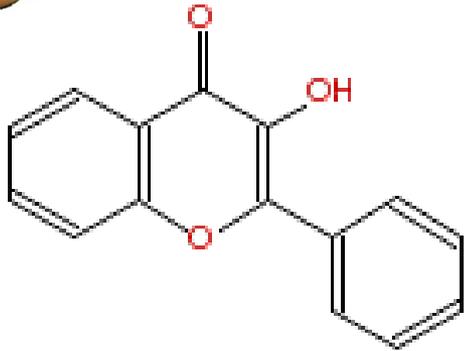
**ABOVE FIGURE IS A FLAVONE**  
**IF R4 is a Ketone group then this is a Flavonoid**  
**IF R3, R4, and double bond C1-C2 = anthocyanin**



Relationships Among Flavonoid Structures



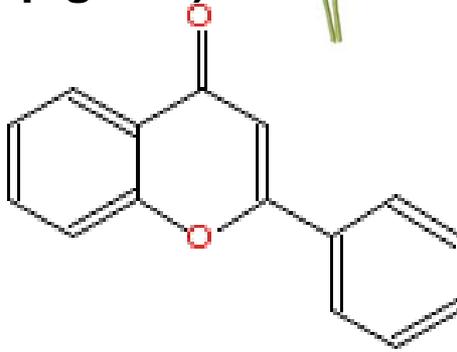
**Onion  
(quercetin)**



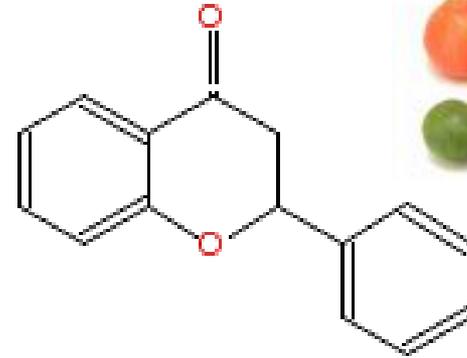
Flavonol



**Parsley  
(apigenin)**

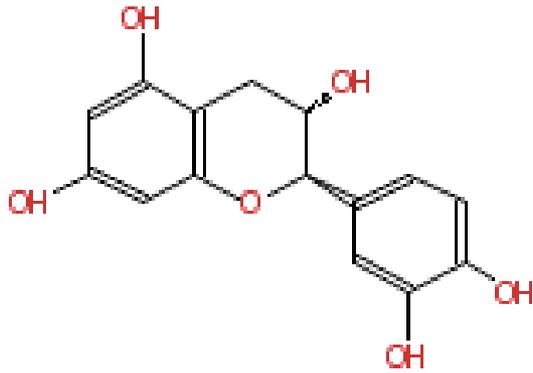


Flavone

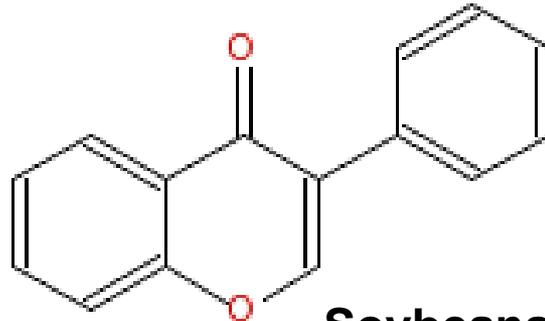


Flavanone

**Citrus  
(naringinin)**

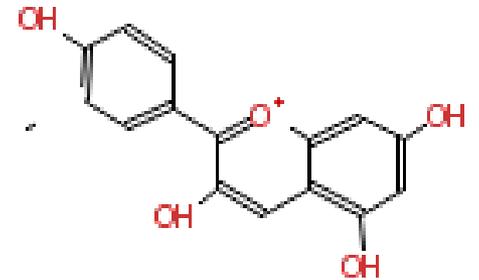


Flavanol (Catechins)



Isoflavone

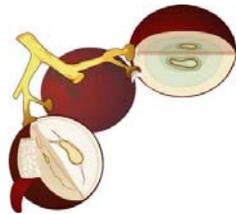
**Soybeans  
(genistein)**



Anthocyanidine



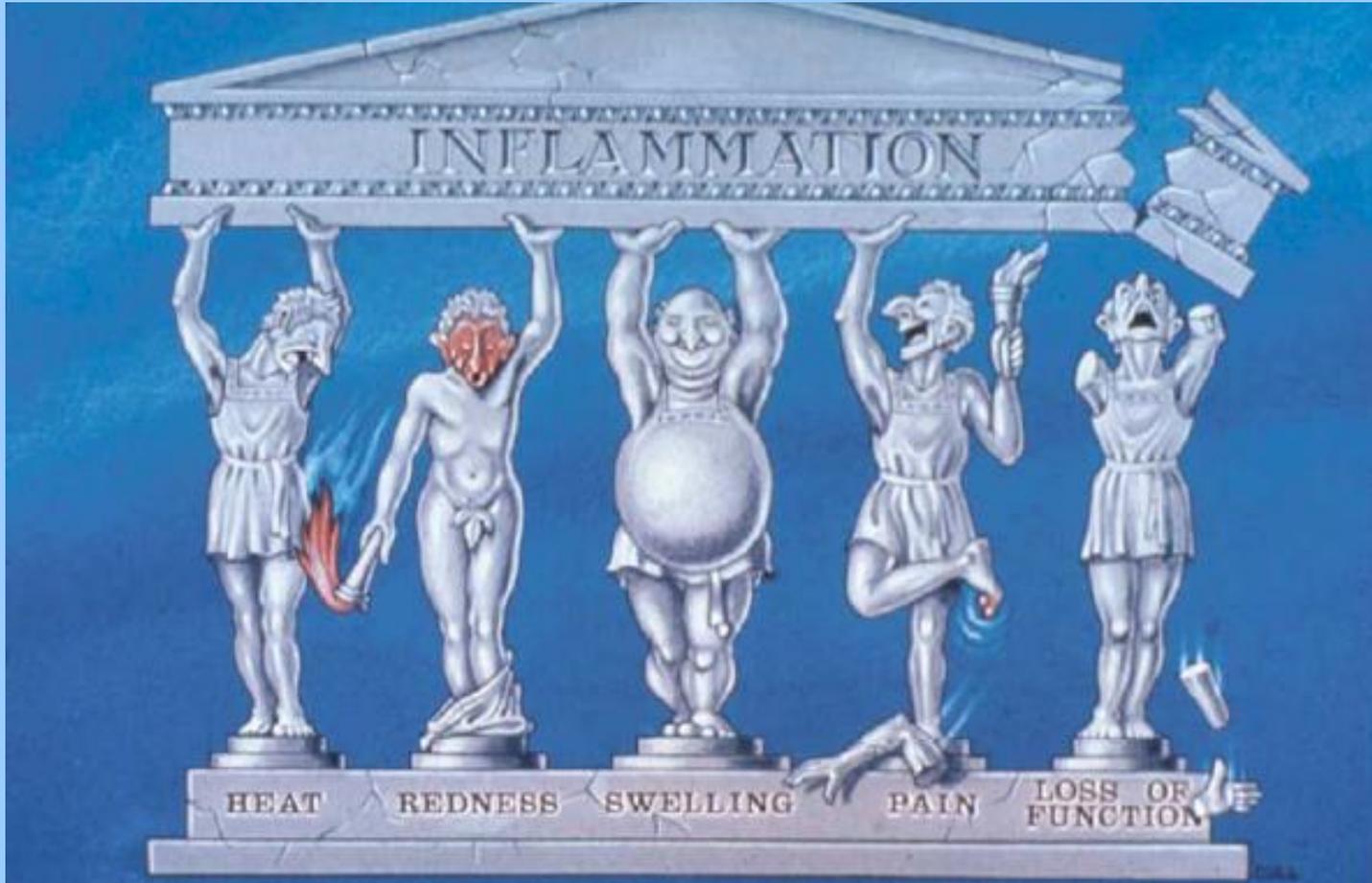
Tea catechins



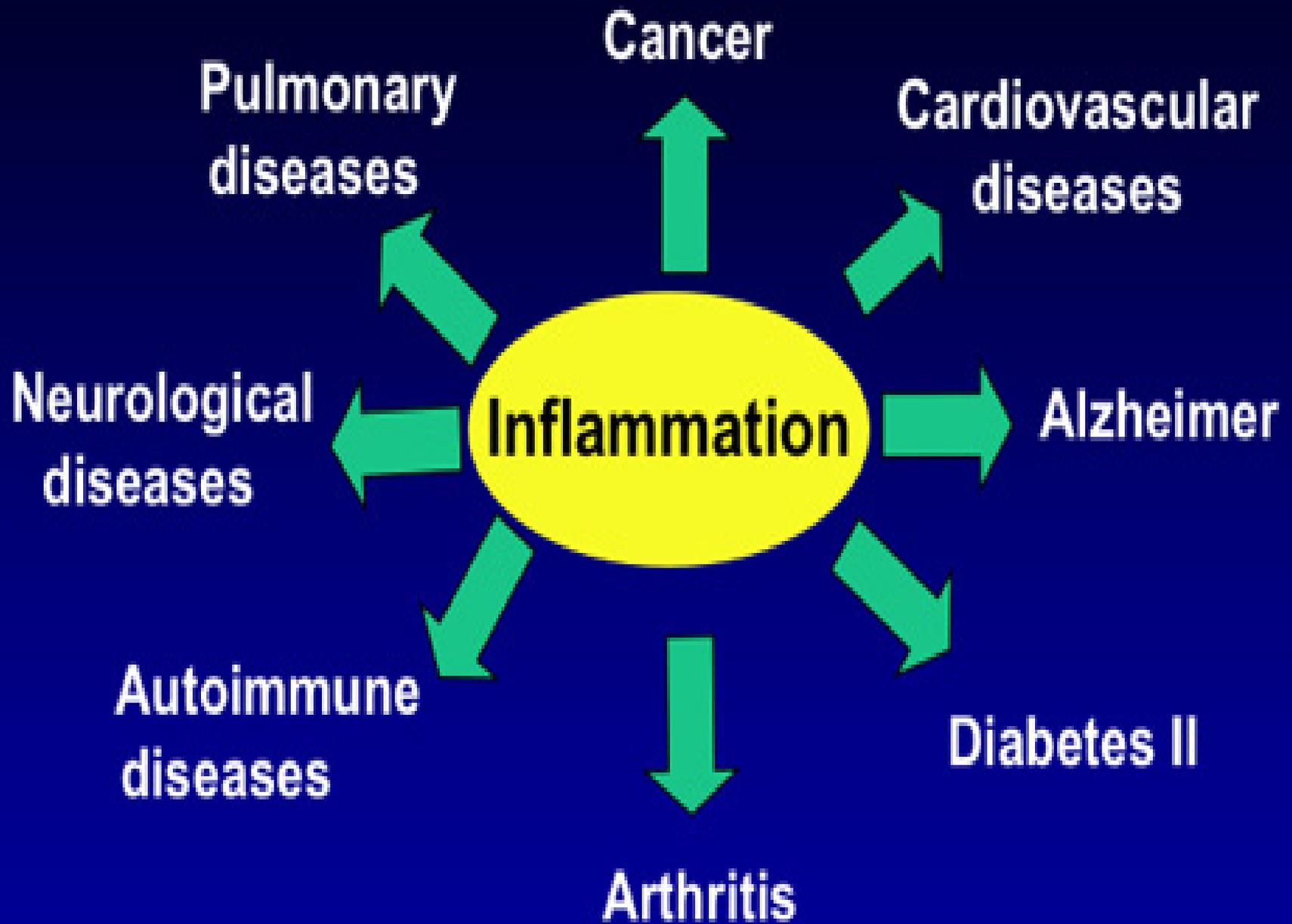
Cocoa and Grape Seed Procyanidins

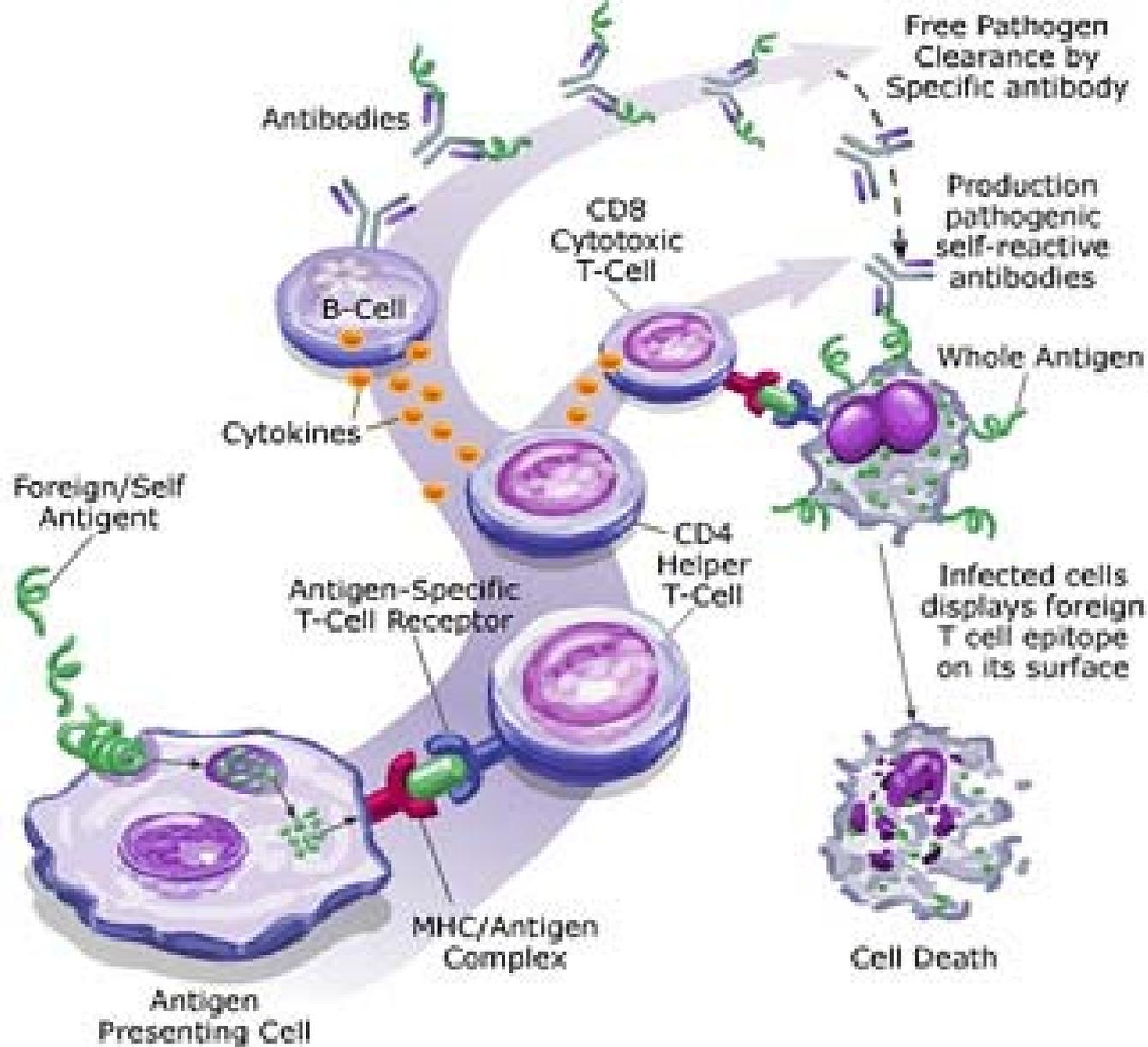


**Berries  
(Pelargonidin)**

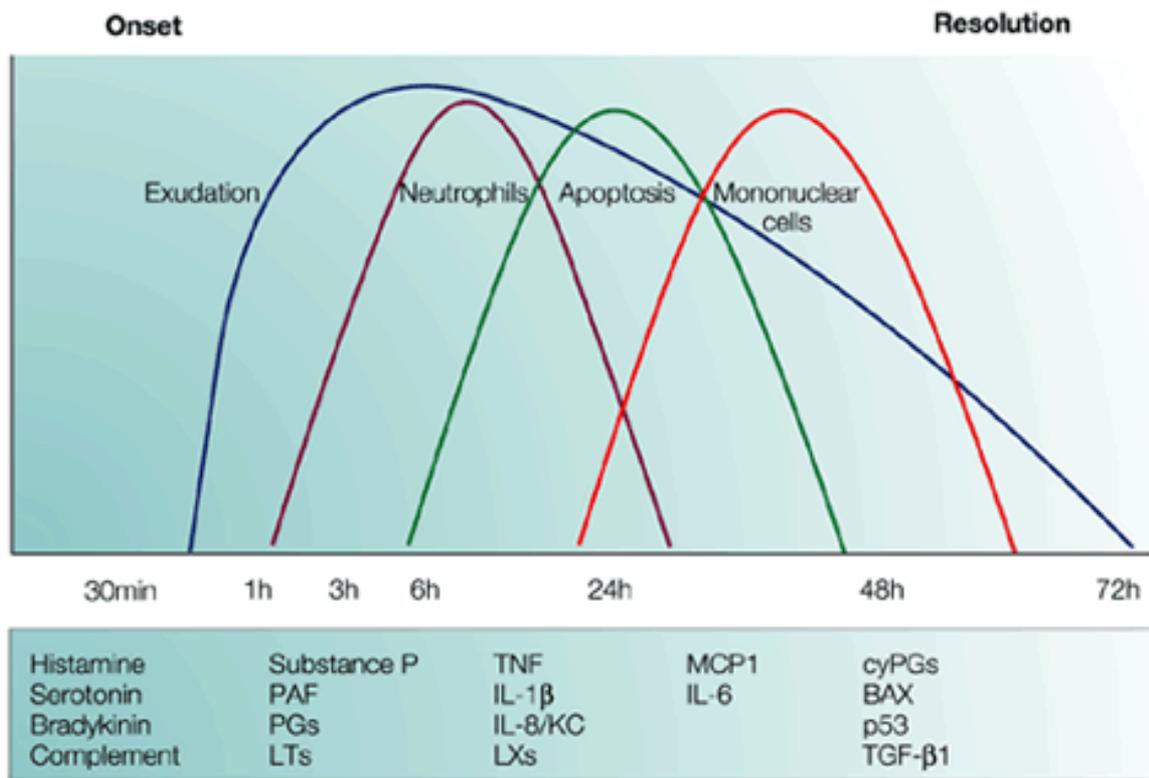


**INFLAMMATION IS A PART OF THE IMMUNE RESPONSE NETWORK THAT IS ESSENTIAL BUT IT CAN BE DAMAGING WHEN SUSTAINED**





**EFFECTIVE INFLAMMATION CLEARS PATHOGENS**



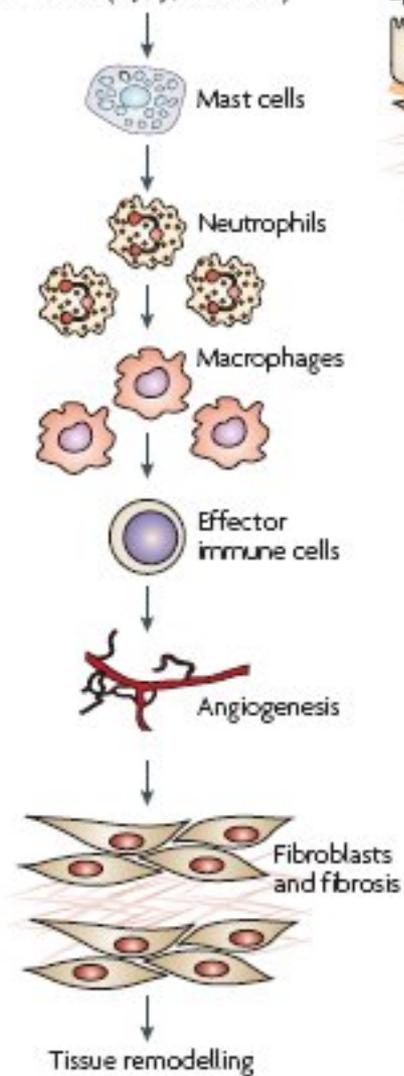
## Cellular time course of inflammation and sequential release of mediators

1. Vasoactive amines and lipid mediators promote exudate formation edema.
2. Expression of cytokines and chemokines.
3. Mononuclear cells phagocytosis promotes release of anti-inflammatory mediators.
4. Failure to clear pathogen (e.g. cancer cell, viruses)  $\rightarrow$  chronic inflammation

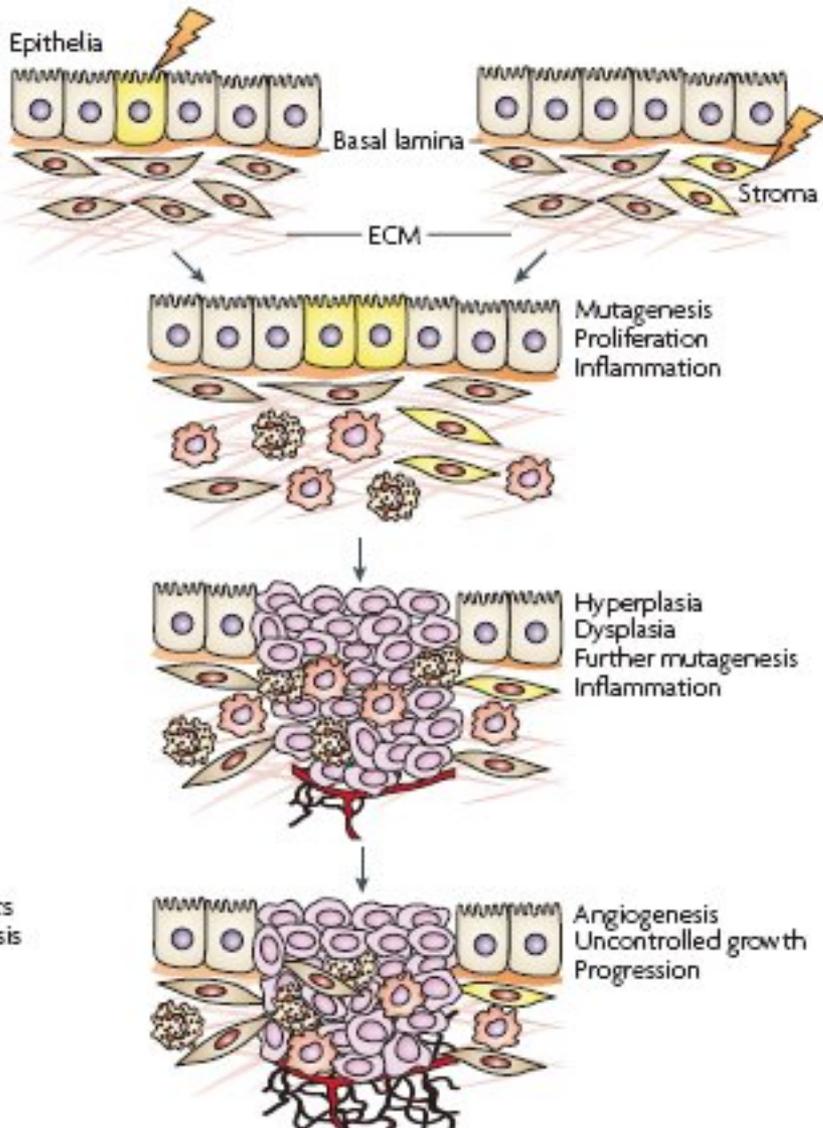


### a Acute inflammation

Stimulus (injury, infection)



### b Carcinogenesis



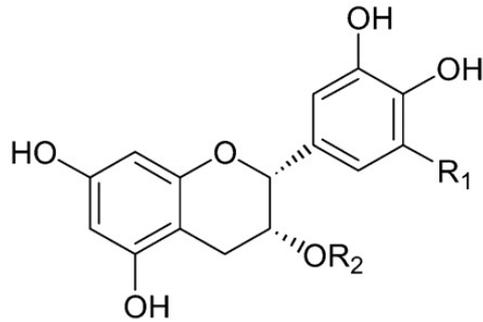
# Examples of Anti-Inflammatory Flavonoids

- Tea Polyphenols  
(Catechins/Theaflavins)
- Grape Seed Extract Procyanidins
- Berry Anthocyanidins  
(Strawberry, Blackberry, Pomegranate)

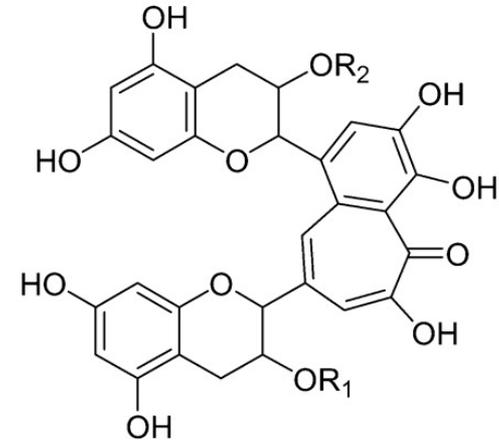


**FIGURE 1 Chemical structure of flavan-3-ols and THE**

FLAVANOLS



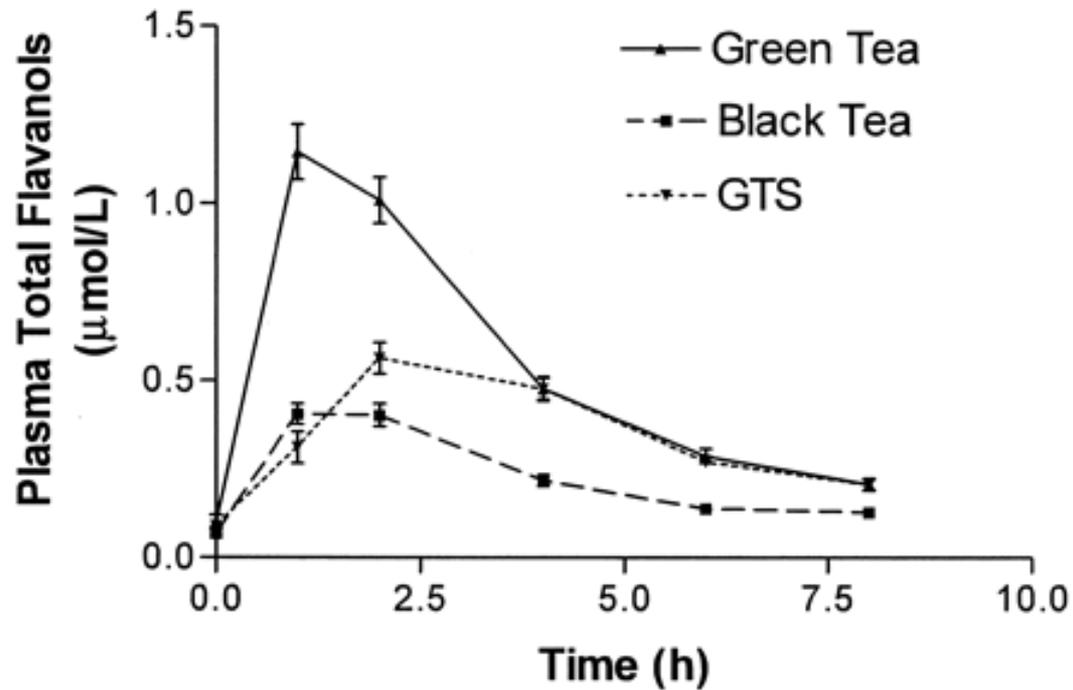
THEAFLAVINS

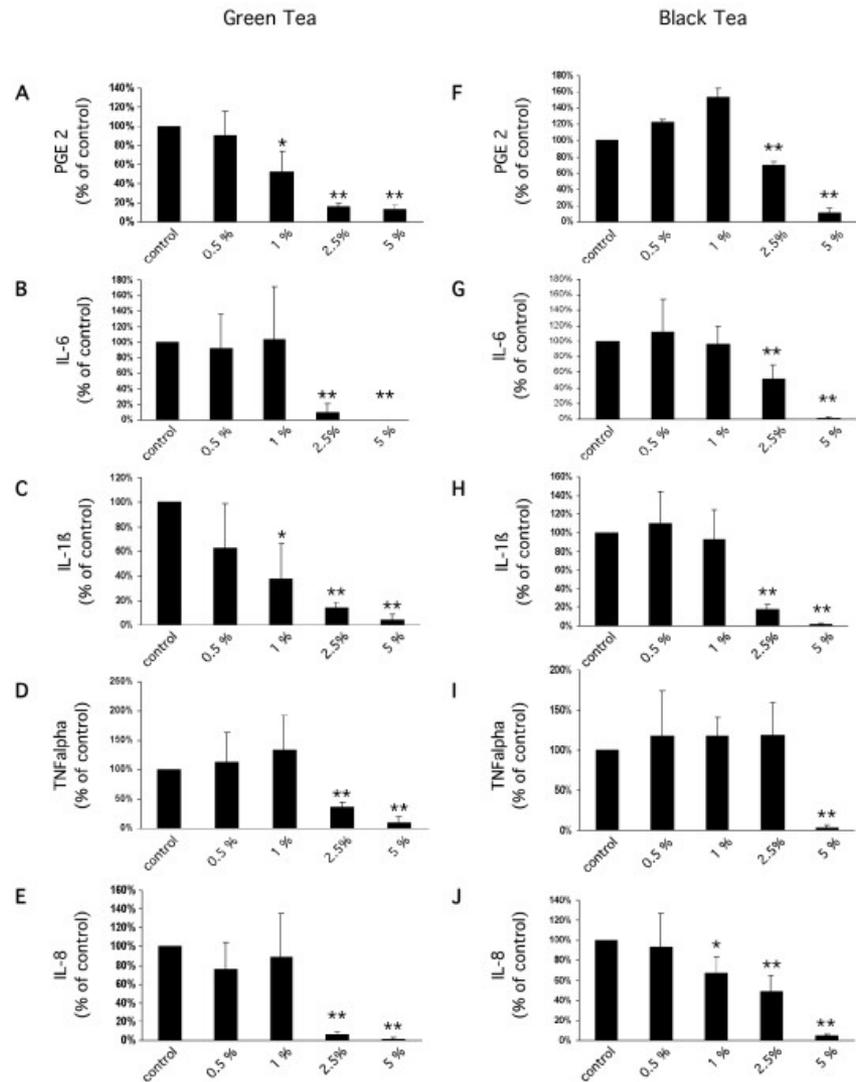


	R <sub>1</sub>	R <sub>2</sub>			R <sub>1</sub>	R <sub>2</sub>
EC	H	H	=	theaflavin	H	H
EGC	OH	H		theaflavin-3-monogallate	gallate	H
ECG	H	gallate		theaflavin-3'-monogallate	H	gallate
EGCG	OH	gallate		theaflavin-3,3'-digallate	gallate	gallate

Henning, S. M. et al. *J. Nutr.* 2008;138:1529S-1534S

# Tea Flavanols are Bioavailable

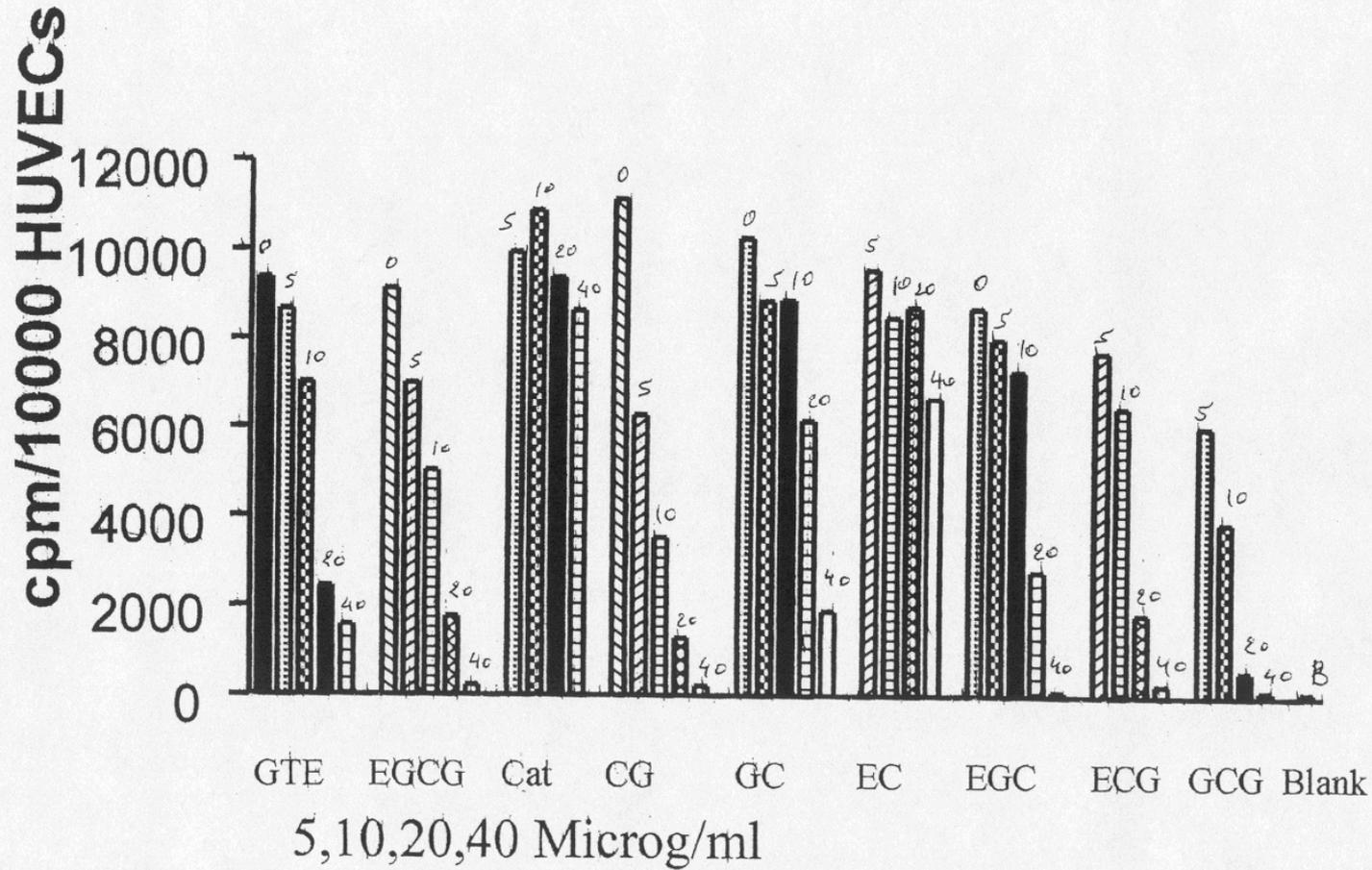


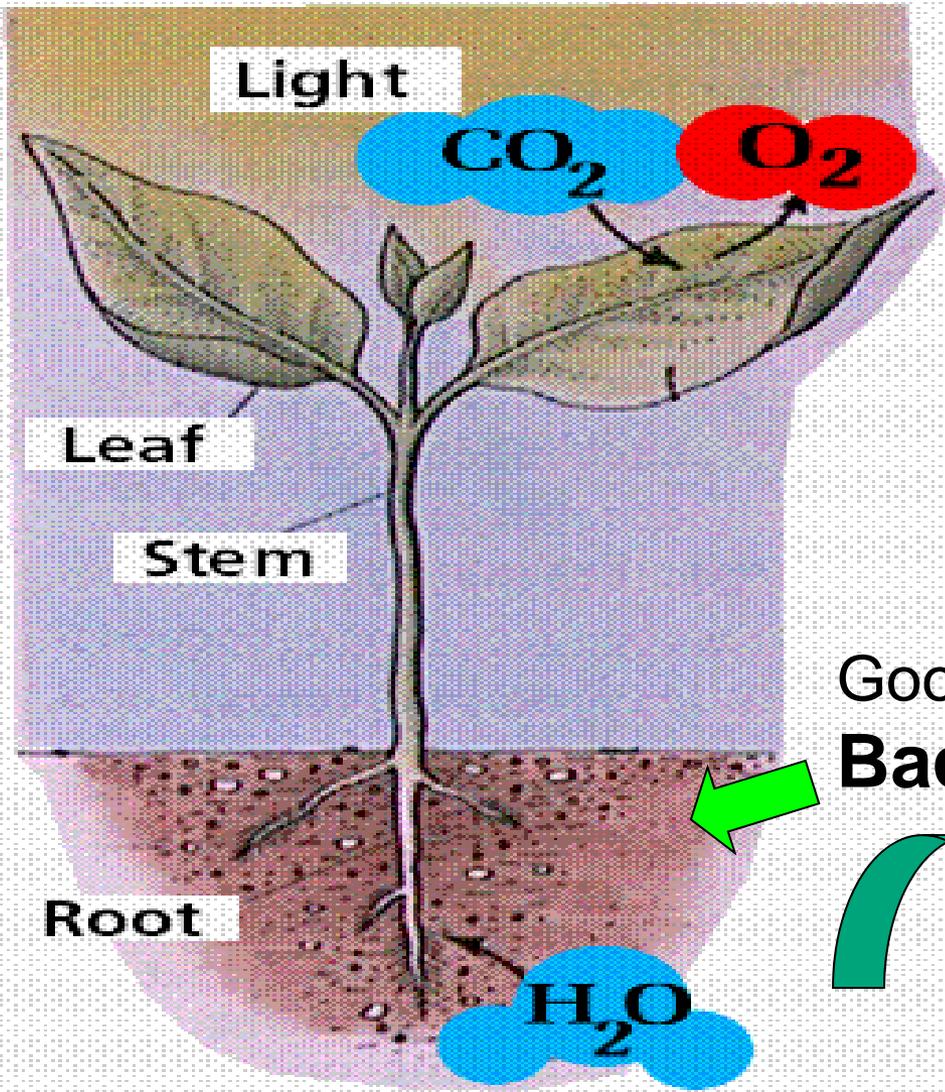


The effects of tea extracts on proinflammatory signaling  
Pajonk, et al. BMC Med. 2006

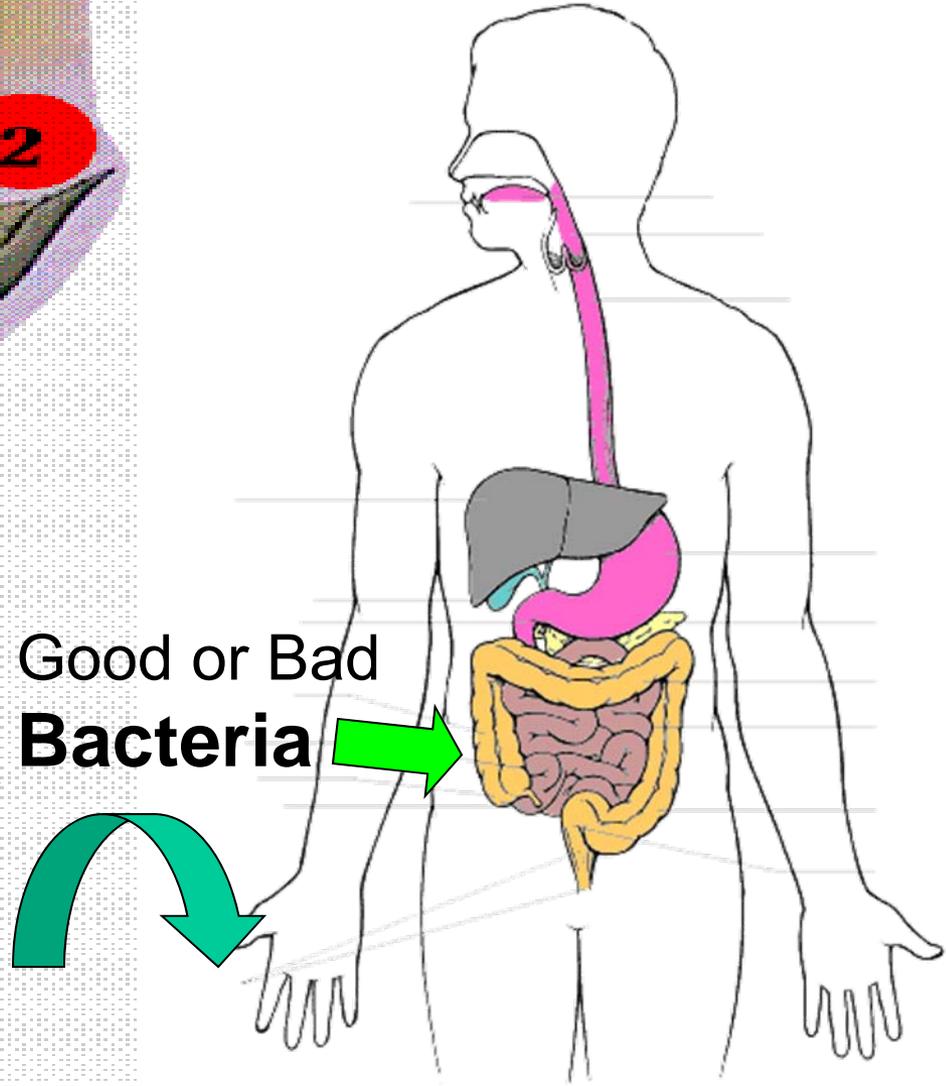
Green Tea and Black Tea Extract Inhibition of PGE-2, IL-6, IL-1 $\beta$ , TNF $\alpha$ , and IL-8  
In LPS-Stimulated Macrophages

# Catechins effect on HUVEC proliferation

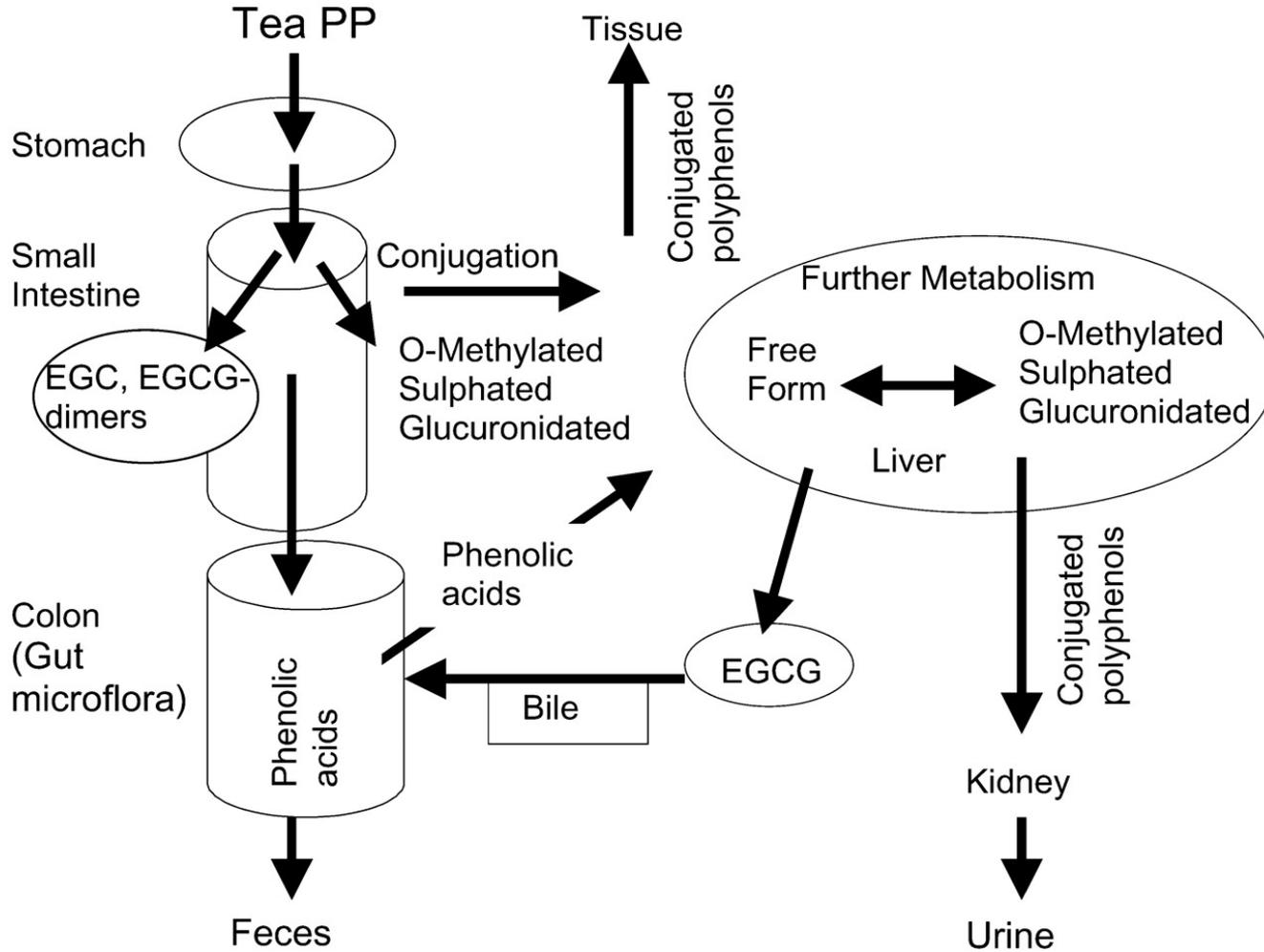




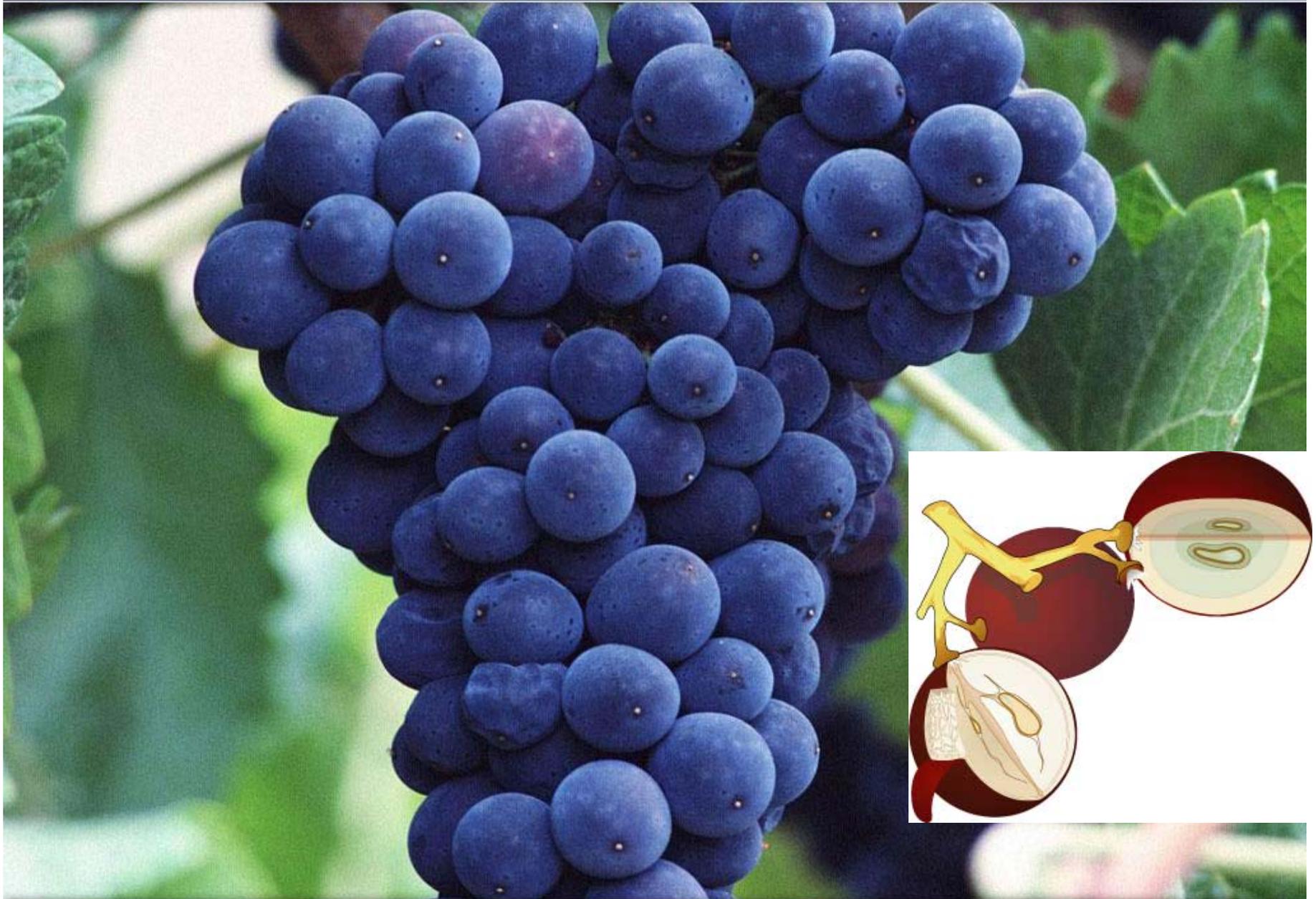
Good or Bad  
**Bacteria**

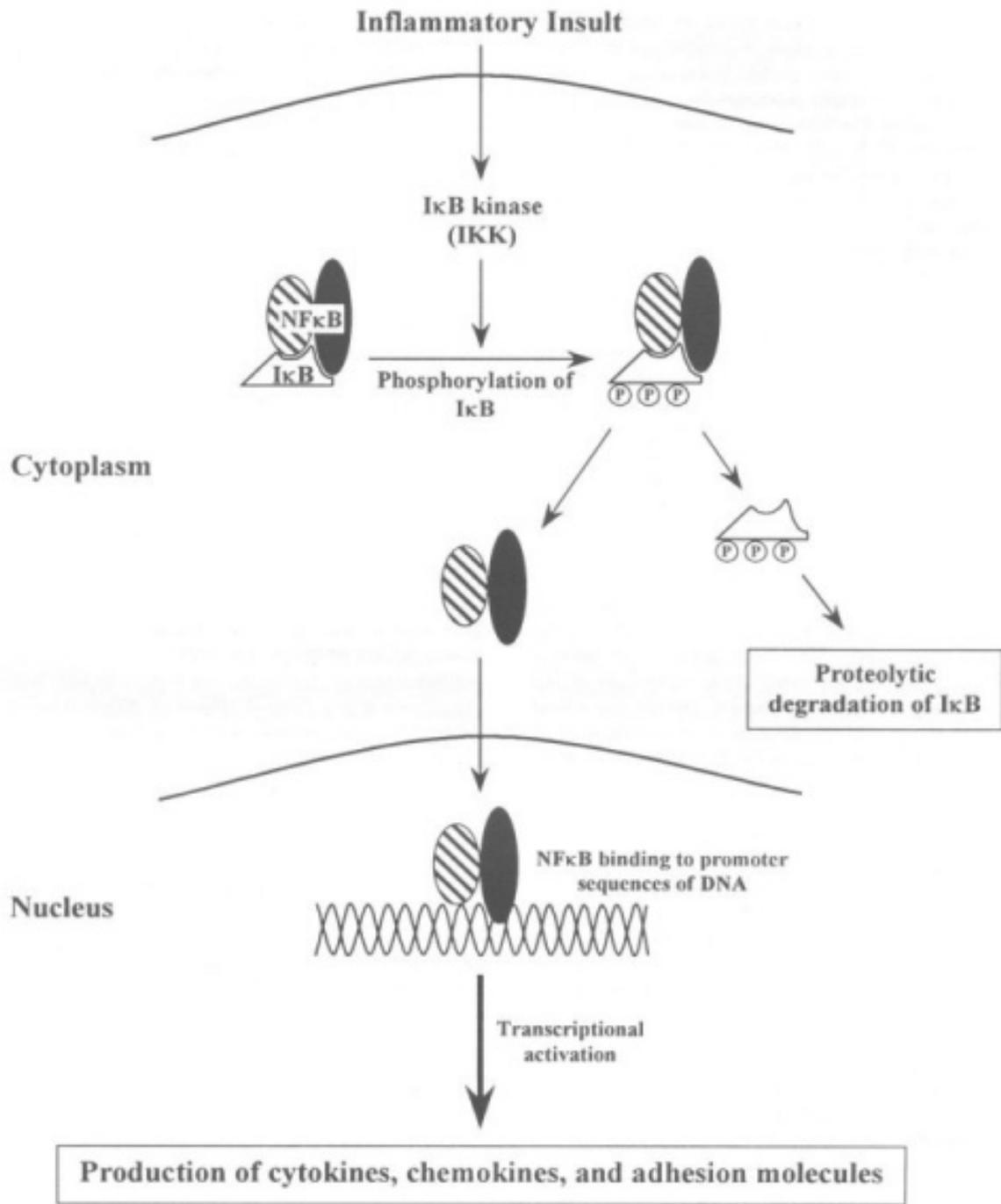


**FIGURE 2 Metabolism of tea flavan-3-ols in the human body**

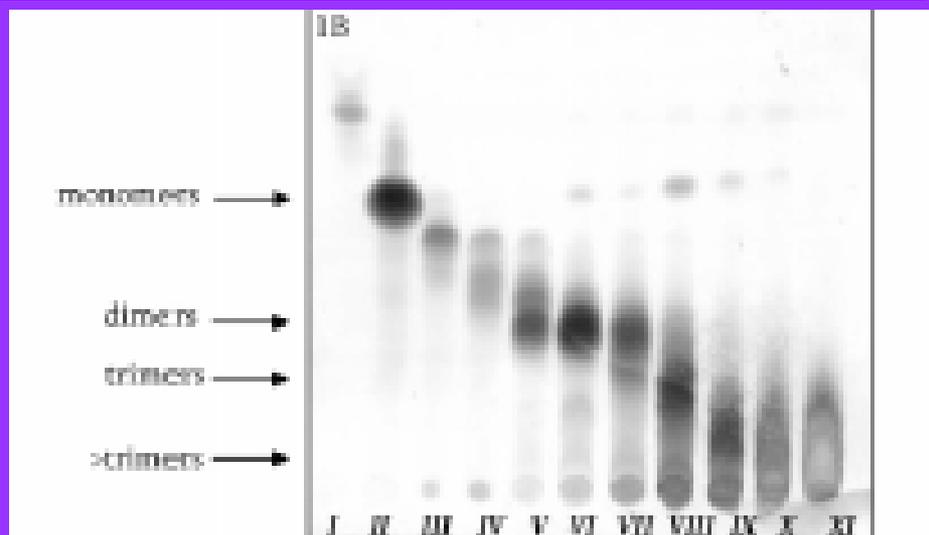
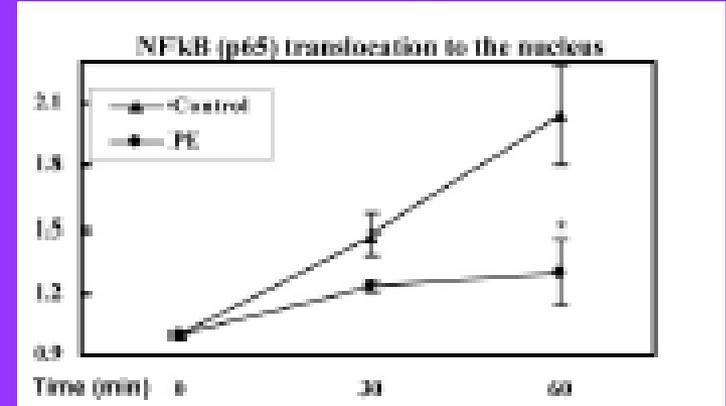
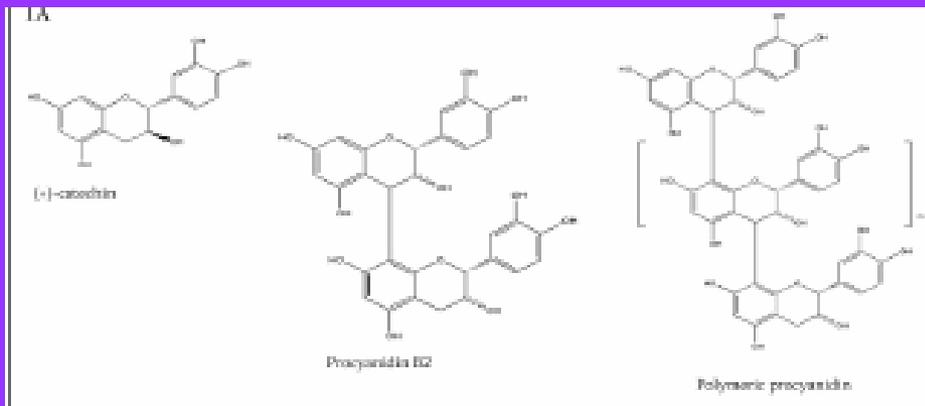


Henning, S. M. et al. J. Nutr. 2008;138:1529S-1534S



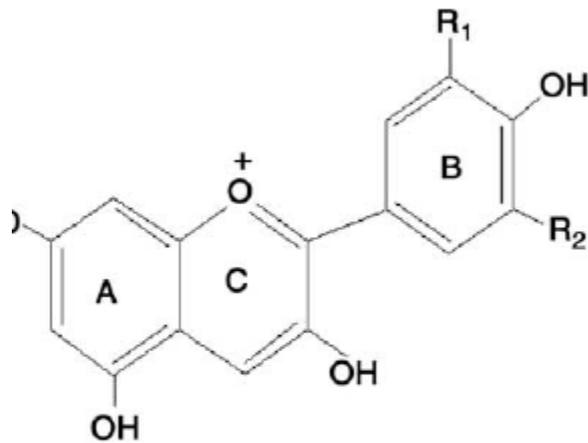


# Grape Seed Extract Procyanidins Inhibit NF- $\kappa$ B

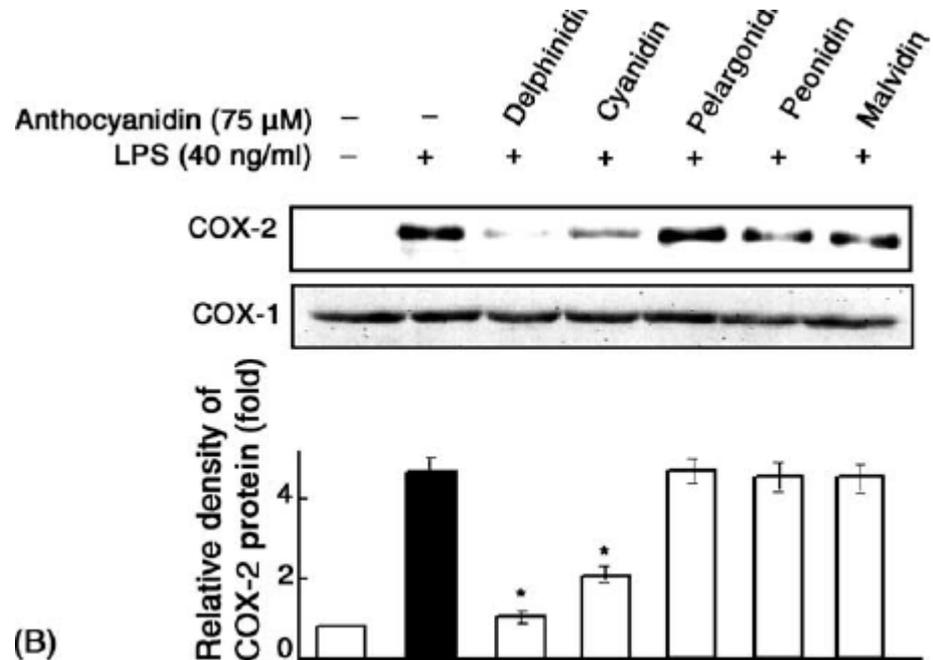


# Anthocyanidins Inhibit COX-2 in LPS-stimulated RAW Macrophages

5) 417-425



Anthocyanidin	R1	R2
Delphinidin	OH	OH
Cyanidin	OH	H
Pelargonidin	H	H
Peonidin	OCH3	H
Malvidin	OCH3	OCH3



# Molecular Mechanisms

- **Modulation of the cascade of molecular events leading to the overexpression of inflammatory mediators include inhibition of transcription factors such as Nuclear Factor kappa B and AP-1, through the inhibition of protein kinases involved in signal transduction.**
- **Increased antioxidant defenses through activation of the NF-E2 related factor 2 (Nrf2) also contribute to the anti-inflammatory capacity of flavonoids.**

# Conclusions

- Flavonoids represent the most abundant polyphenols in the diet.
- Flavonoids in families are metabolized to other active compounds through actions of the gut flora and the liver.
- Molecular pathways initiated by NF- $\kappa$ B, AP-1, and Nrf2 are inhibited by flavonoids commonly.
- More research is needed on the in vivo effects of flavonoids on inflammation and chronic diseases in humans .
- These insights should influence public policy on nutrient-dense foods such as fruits,vegetables,and nuts to promote intake of these healthful foods.