Natural products and chronic pain

TTUHSC 2019 Collaboration Across Pain Science & Practice

IMS Symposium

4th Annual Symposium of the Center of Excellence for Translational Neuroscience and Therapeutics (CTNT)

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Chronic pain – National Center for Complementary and Integrative Health

Institute of Medicine – USA 2017
https://nccih.nih.gov/news/multimedia/infographics/chronic-pain

100 million People suffer from chronic pain

Costs - $560-635 billion annually (other estimates in $trillions) for health care and lost productivity
A major cause of loss work
Chronic pain is described as > 12 weeks

Unique to each person: complex physiology and psychology

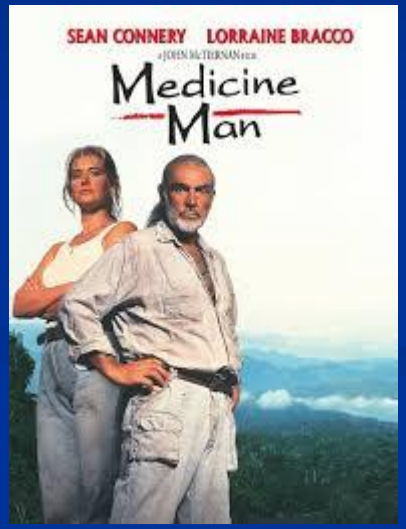
Chronic pain – National Center for Complementary and Integrative Health

Institute of Medicine – USA
https://nccih.nih.gov/news/multimedia/infographics/chronic-pain

Back pain, neck, joint, arthritis, migraine

Chronic pain contributes to trouble sleeping, locomotive problems, fatigue, depression, anxiety, reduced quality of life and negative changes to the brain

Factors: Lifestyle, diet, genetics, disease state



Age, pain, physical fitness and activity

Greg Alan Maddux traded by Chicago to Los Angeles in August 2006

Maddux (Mad Dog or Professor), who spent his first seven seasons with the Cubs, returned to Chicago before the 2004 season after 11 years with the Atlanta Braves. He got his 300th win and 3,000th strikeout with the Cubs.

Born in 1966.
Signed in 1984 with the Cubs.
Retired after the 2008 season.

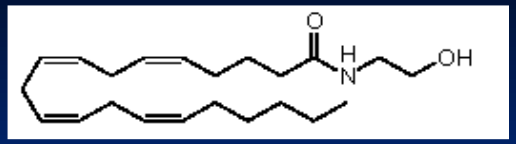
Maddux is known for his sense of humor and keen wit. Upon walking into the Braves clubhouse during 2003 spring training, Maddux saw doughnuts bought from a local grocery store and said "Where's the Krispy Kreme? How do they expect us to play like champions if they don't feed us like champions?"

Aging and active lifestyle – adapting to age and pain

- Distance running

- Motorcycle trails, motocross

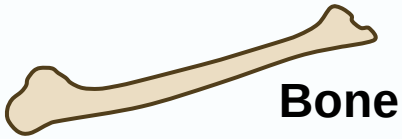
Endocannabinoids (eCB), exercise, pain (Watkins 2018)



- increased circulating levels of eCB after exercise, some eCB exert analgesic effects from exercise
- Exercise is a area of investigation to explore hypotheses to explain the mechanisms for cognitive benefits in young and older adults.
- AEA (n-6 PUFA) increases in blood after moderate and intense aerobic exercise – Will animal derived NP (n-3 PUFA) alter these responses?
- In many respects, the responses of wheel exercise in mice demonstrating increased levels of eCB in blood, neuroplasticity, and improved behavior; appear to occur to some extent for exercise in the human.
- New investigations on the endocannabinoid system (ECS) to explain its role in well-being and improved quality of life in later years should focus on controlling pain.
- The ECS, its collective components, are widely found in the CNS and peripheral system, as well as the immune system. The ECS is clearly involved in pain and the neuro-inflammatory pathways associated with pain.
- Evidence that NP, e.g. terpenoids, acts via pathways of the ECS.

The endocannabinoid system (ECS) is ubiquitous – influence on multiple systems related to pain, inflammation, homeostasis & anabolic pathways

(Watkins & Kim, Frontiers in Psychology 2015: doi: 10.3389/fpsyg.2014.01506)

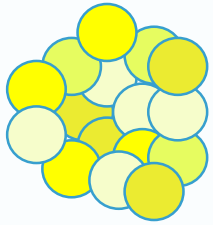


Bone

-Modeling/Remodeling

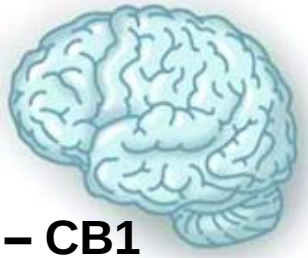
Skeletal Muscle

-Glucose homeostasis



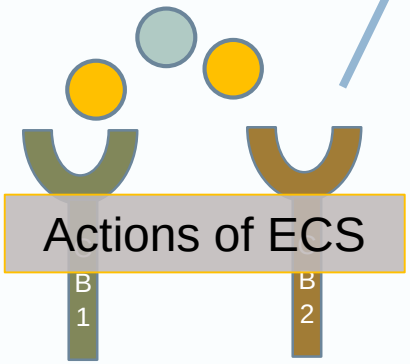
Adipose Tissue

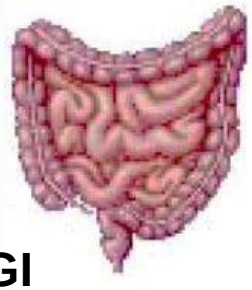
-Lipid metabolism



Brain – CB1

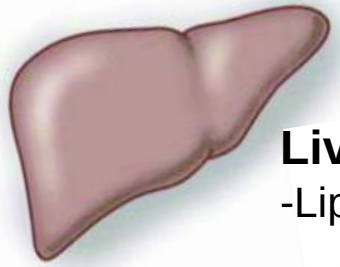
-Mood
-Cognition
-Reward
-Sleep
-Neuroprotection
-Appetite





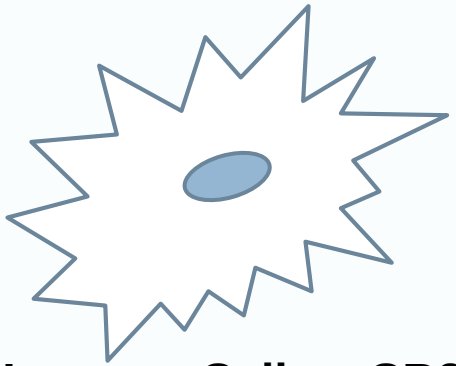
GI

-Anorectic signals



Liver

-Lipid metabolism



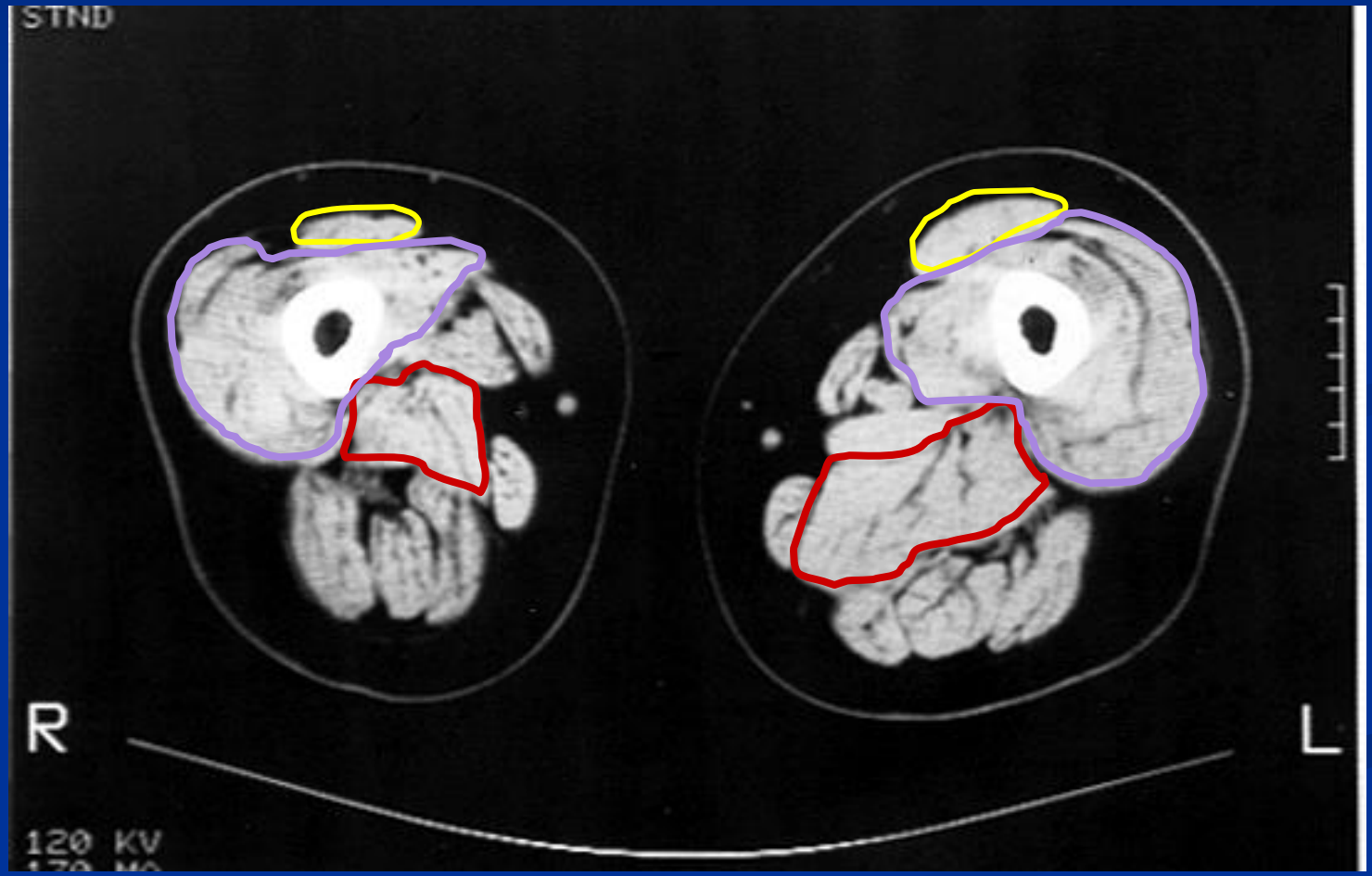
Immune Cells – CB2

-Monocyte differentiation
-inflammation

Uncontrolled pain, disease, disuse atrophy (rt. muscle), chronic joint pain, inflammation

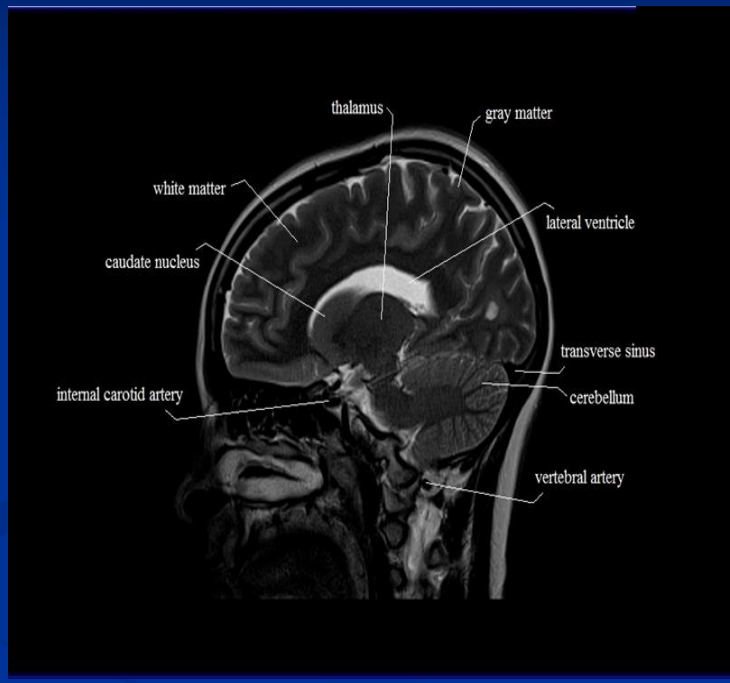
49-year-old man with painful pelvic bony metastasis which prevented weight bearing on right hip and leg.

http://www.cu2000.med.upenn.edu/Radiology/Troupin/int8view3.html



Acute and chronic pain – Apkarian et al. 2005

- acute pain perception in normal subjects is to some extent different from that in chronic clinical pain conditions; chronic pain engages brain regions important for cognitive/emotional assessments
- nociceptive system is recognized as a sensory system including primary afferents to multiple brain areas – pain perceived by dynamic interactions of ascending and descending pathways
- chronic clinical pain conditions more frequently involve PFC (prefrontal cortex), while in normal subjects perception of experimental pain more frequently involves primary & secondary somatosensory cortex, thalamus, & anterior cingulate



Natural products – diversity of phytochemicals and plant bioactives (classified as naturally occurring toxicants)

Bioactivity – phenolic, polyphenolic compounds; isoprenoids

Example of polyphenolic compounds (secondary metabolites of plants) – coumarins, flavonoids (quercetin) [flavones, flavonols, flavonones, flavanols, anthocyanidins], isoflavonoids, lignans, phenolic polymers (tannins)

Phenolic acids, gallic acid, and isoflavones are easily absorbed as are catechins and quercetin glucosides
Terpenoids (isoprenoids) – related to carotenoids

Large polyphenols like proanthocyanidins are poorly absorbed, these are degraded before being absorbed

Generally during (phase II) absorption polyphenols undergo biotransformation (phase I cyto P450 and phase II enzymes influenced by diet composition in rodents)

Thus, the structure of resulting metabolites could be completely different from the parent compound and may not affect biological actions.

Natural products – potential in vivo effects of phytochemicals and plant bioactives depends on physiology and metabolism (Cassidy & Minihane, 2017)

Oral route

Bioavailability

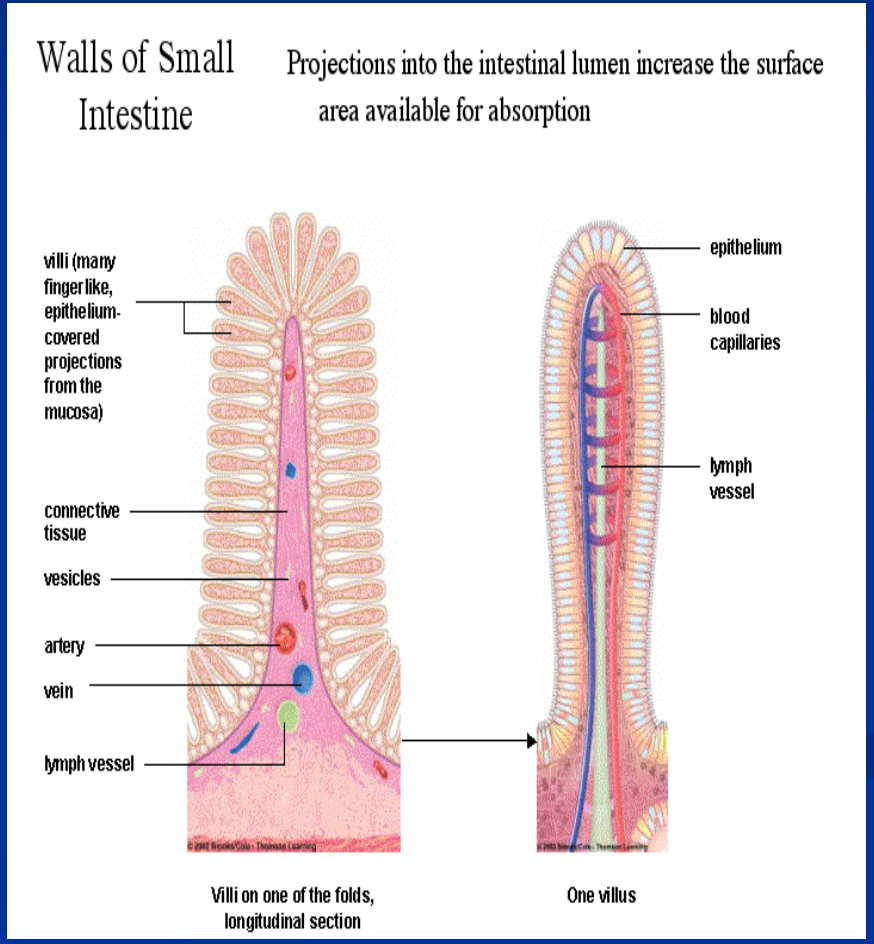
Intake versus amount assimilated

Bioaccessibility

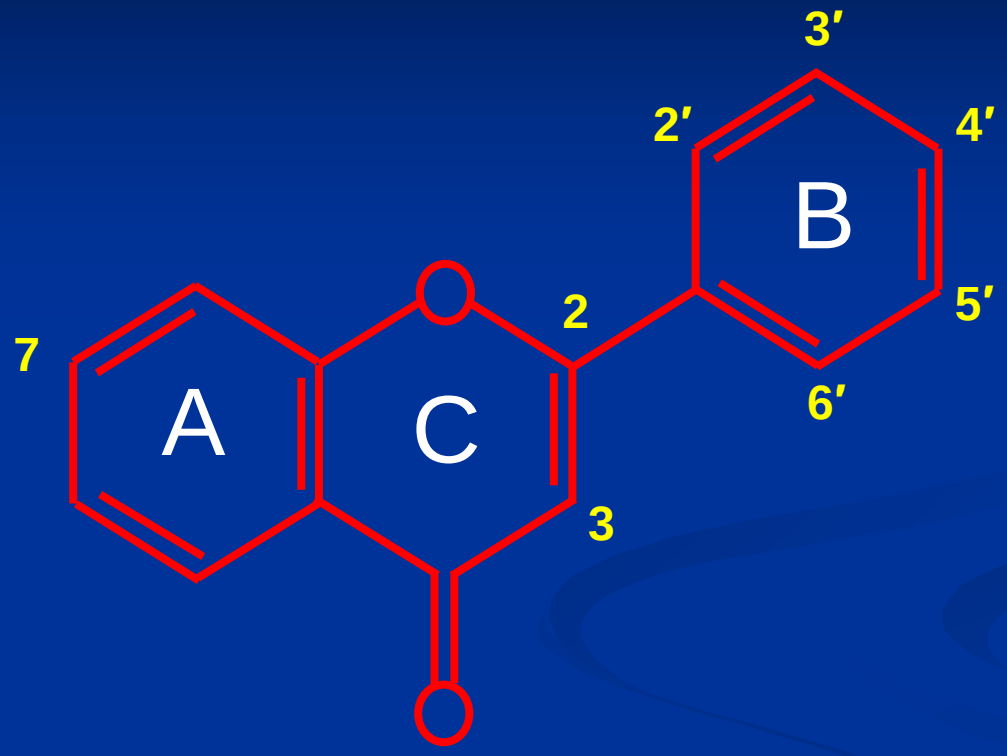
Actions of digestive transformation of bioactive compounds (gut microflora) (use of Caco-2 cells)

Bioactivity

Transport and assimilation to target tissue; metabolism or biotransformation biomarker
Physiological response



Chemical Structure of Flavonoids (Flavone aglycone)
Isoflavones (genistein and daidzein) the B-ring is attached at position C-3 (B-ring attached to C-2 of C-ring in flavonoid)



A and B: benzene rings; C: pyran ring;
glycoside (sugar at C-3 or C-7)

Natural products – potential in vivo effects of phytochemicals depends on absorption, distribution, metabolism, and elimination

Bioactivity - Cardiovascular system and target tissues

Metabolites reaching the blood may be different than the original compounds (gut and hepatic metabolism, Cassidy & Minihane, 2017)

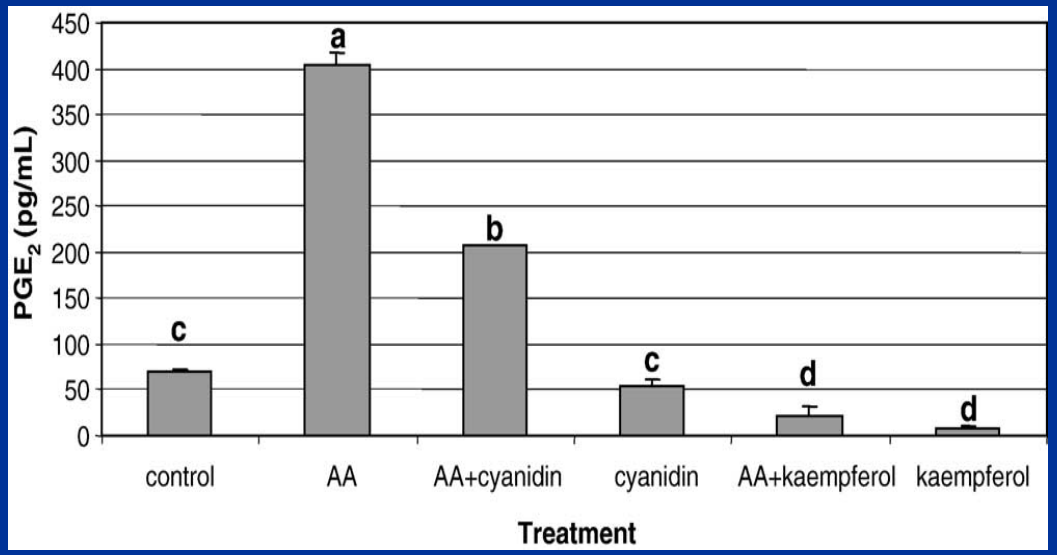
In vitro results such as cell culture systems may be different than in vivo effects – thus strengths and limitations of all research approaches should be considered

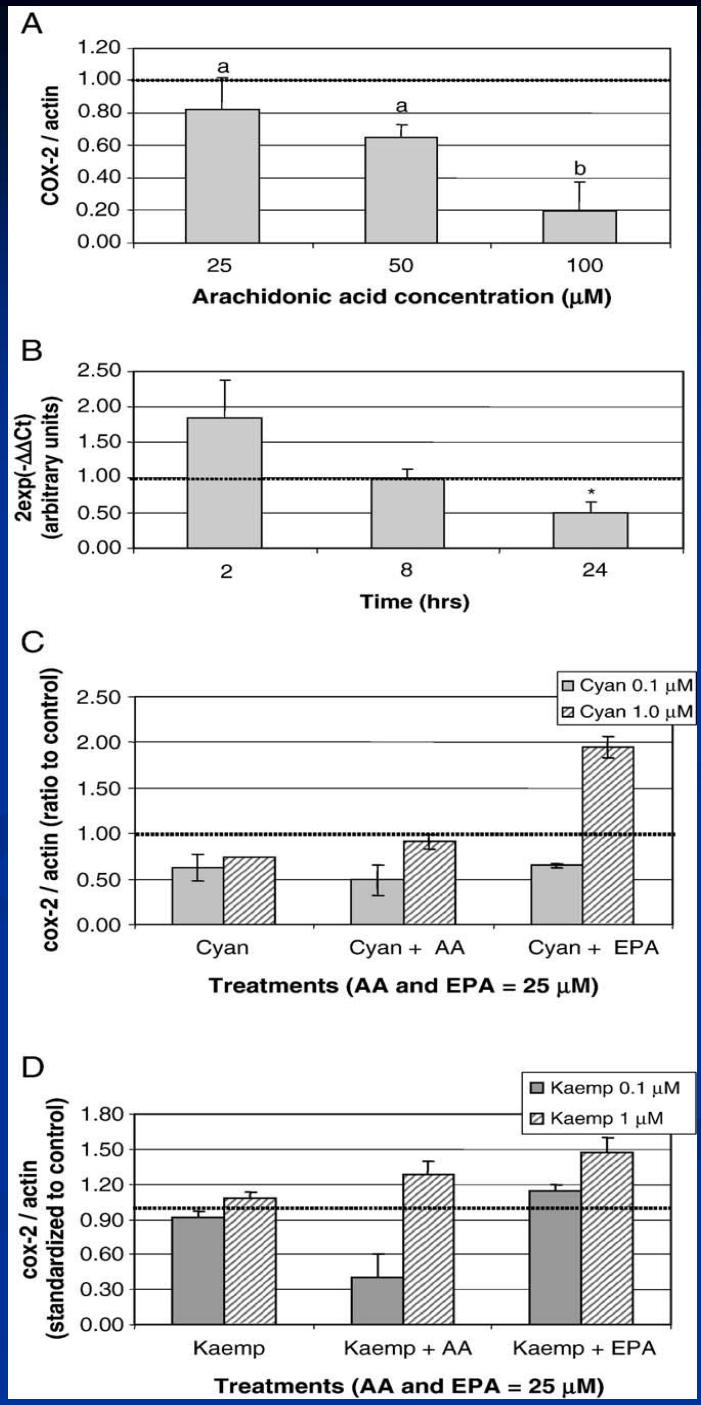
Other factors in animal research are diverse composition of diets and the ingredients used by investigators affect outcome (Rucker and Watkins, 2019)

Important considerations for polyphenolic cpds and determination of biomarkers and physiological responses (e.g. antioxidant, anti-inflammatory)

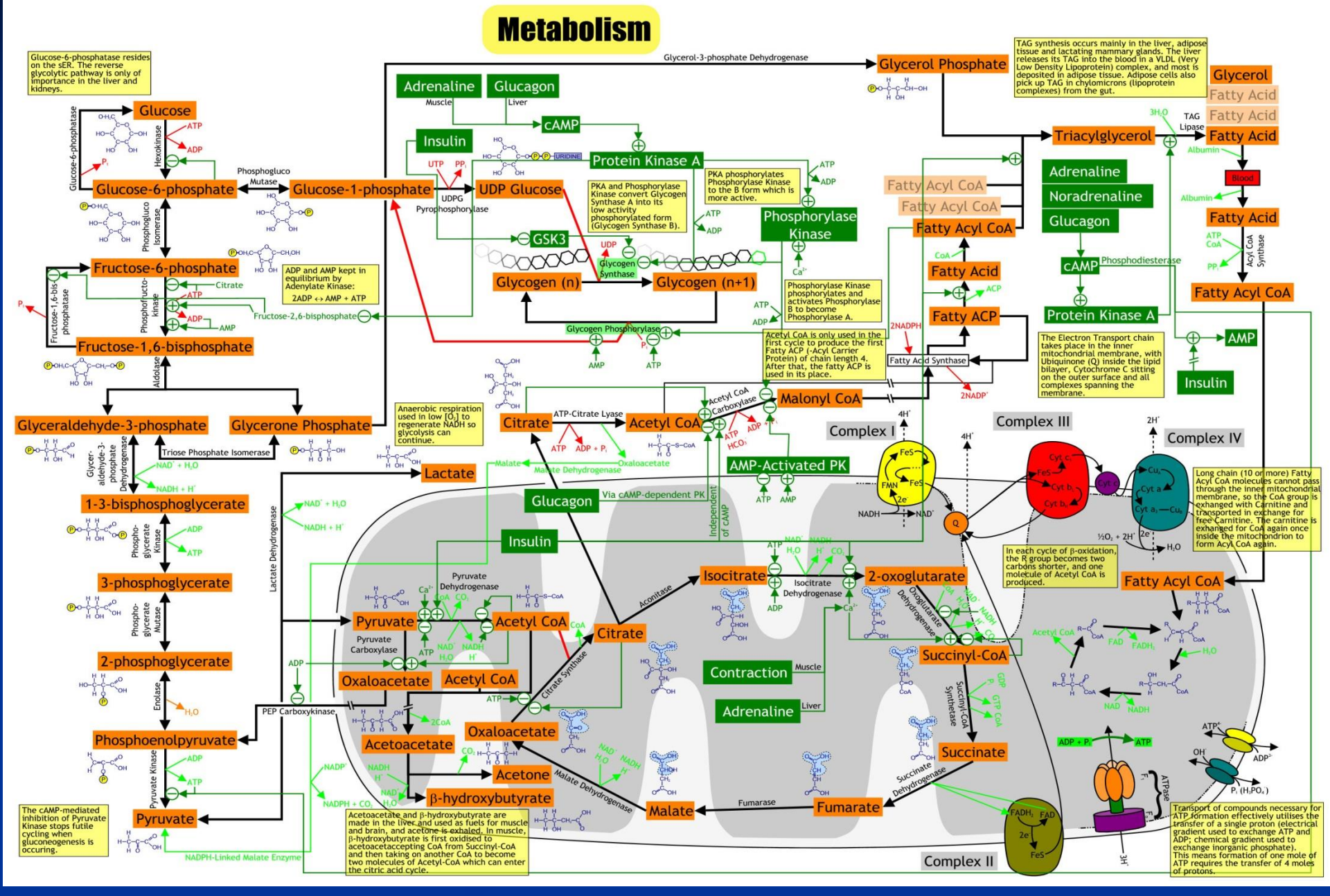
Flavonoid actions on PGE_2, COX-2 protein & mRNA, and NF-κB in cancer cell cultures

(Muñoz-Espada & Watkins 2006; Horia & Watkins, 2007)





Metabolic flux



Natural products – effects on pain (Quintans et al. 2014)

Analgesic properties of natural products - **Review of studies in mice and rats**

Studies using flavonoids, terpenoids, alkaloids, phenols, & carotenoids.
Products purchased commercially (58%) and other compounds isolated from plants (41%), secondary plant metabolites. Injected.

Animal models used in neuropathic pain: PSNI, streptozotocin-induced diabetes, CCI, alcoholic neuropathy, MIA and neuropathic pain induced by paclitaxel.

Mechanisms investigated included prot. kinase C, antioxidant activity, anti-inflammatory actions (cytokines, expression of KF-κB), involvement of opioid and dopaminergic systems, nitric oxide pathway, & activation of cannabinoid receptors and interaction with TRPV1/TRPA1 receptors.

The authors describe the NP as derived from medical plants.
Herbal medicines reported beneficial in management of painful neuropathy.
Use in China is 40% of NP linked to traditional medicine.

Natural products – effects on pain (Quintans et al. 2014), continued

Analgesic properties of natural products - Review of studies in mice and rats

Flavonoids are pharmacologically active in humans, their activity in neuropathic pain is linked to antioxidant and altering prot kinase C

Terpenoids can cross the blood brain barrier to influence the CNS, the cpds appear to modulate neurotransmitters such as glutamaterigenic, serotoninergic, opioid, and cannabinoid (endocannabinoids Janero & Makriyannis, 2014).

Alkaloids – action on the CNS from indole alkaloids a requisite for analgesia, lappaconitine (terpene-alkaloid diterpenoid) appears to have analgesic effect & some potent neurotoxin action

Studies with **terpenes** in ligation of sciatic nerve demonstrated benefits via activation of cannabinoid receptors (CB1 and CB2). [terpenes & ECS reviewed by Janero & Makriyannis 2014].

Natural products – effects on pain (Gouveia et al. 2018)

Cancer pain **-** ***Morphine first NP compound extracted (opium)***

examined 15 different NP used in preclinical studies (terpenes class, mono- and di-, tri-), flavonoids (quercetin, morin and epigallocatechin-3-gallate) and alkaloids

THC pure or associated with CBD, examined in 3 clinical studies of advanced-stage cancer (target cannabinoid receptors, CB1 and CB2)

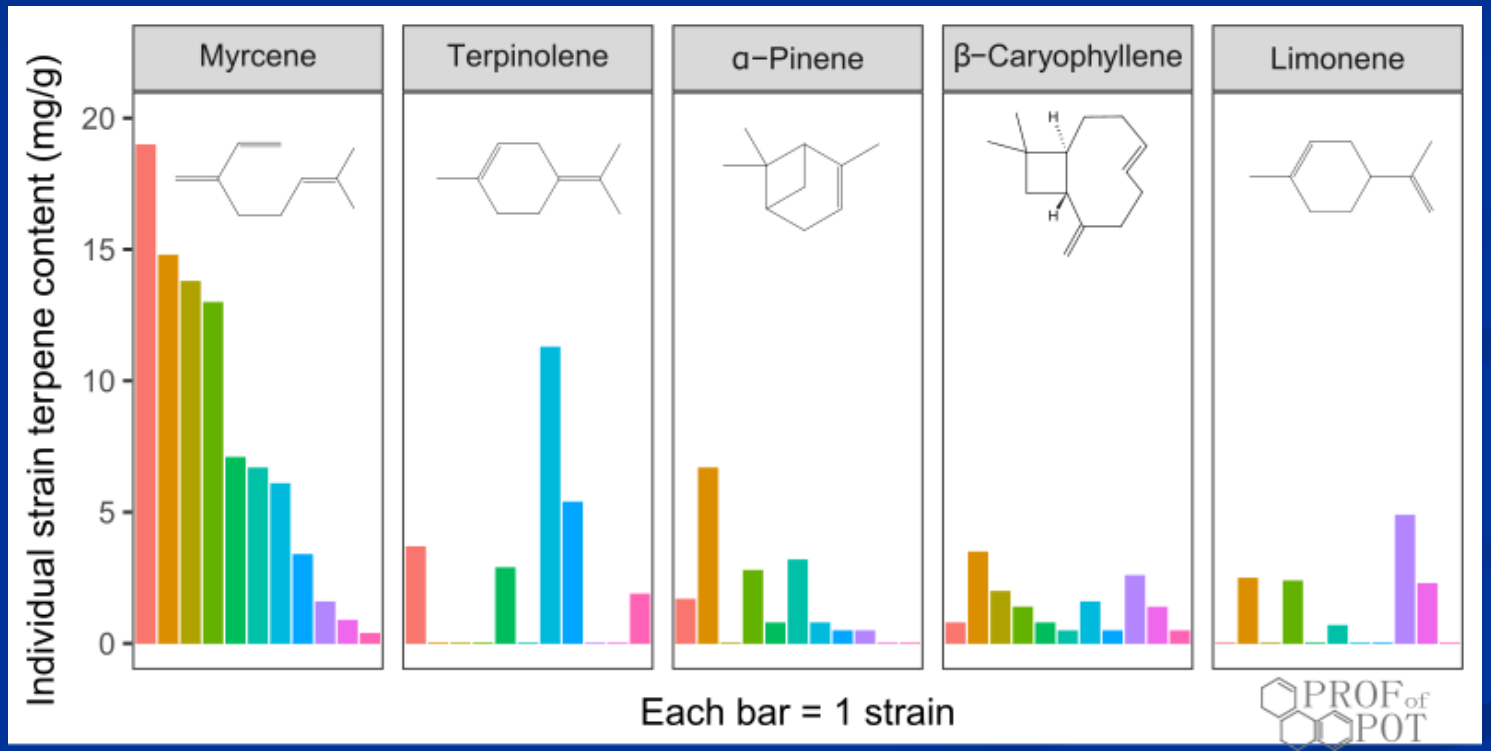
Carvacol (monoterpene) improved hyperalgesia and reduced oncology nociception activating the CNS in mice; responses were more effective for improvement of bioavailabilty of the active compound

Carvacol inhibits pain by altering TRPV3 and TRPA1 channels (pain control) and chemical properties of antioxidant and anti-inflammatory processes [reduction of NO, cytokines, arachidonic acid (COX, LOX pathways, oxylipins)], reduced inflammatory actions (actions on IL-10)
Other compounds (quercetin) that show antinociceptive effects in rodent models of cancer pain (inhibition of IL-1β and TNF-α)

Natural products – Terpenes & ECS (Janero & Makriyannis 2014)

G-protein coupled receptors and transicent receptor potential (TRP) cation channels, pleiotropic for diverse ligands (terpenes and eCB) – CB1 and TRPV1 are co-expressed in brain

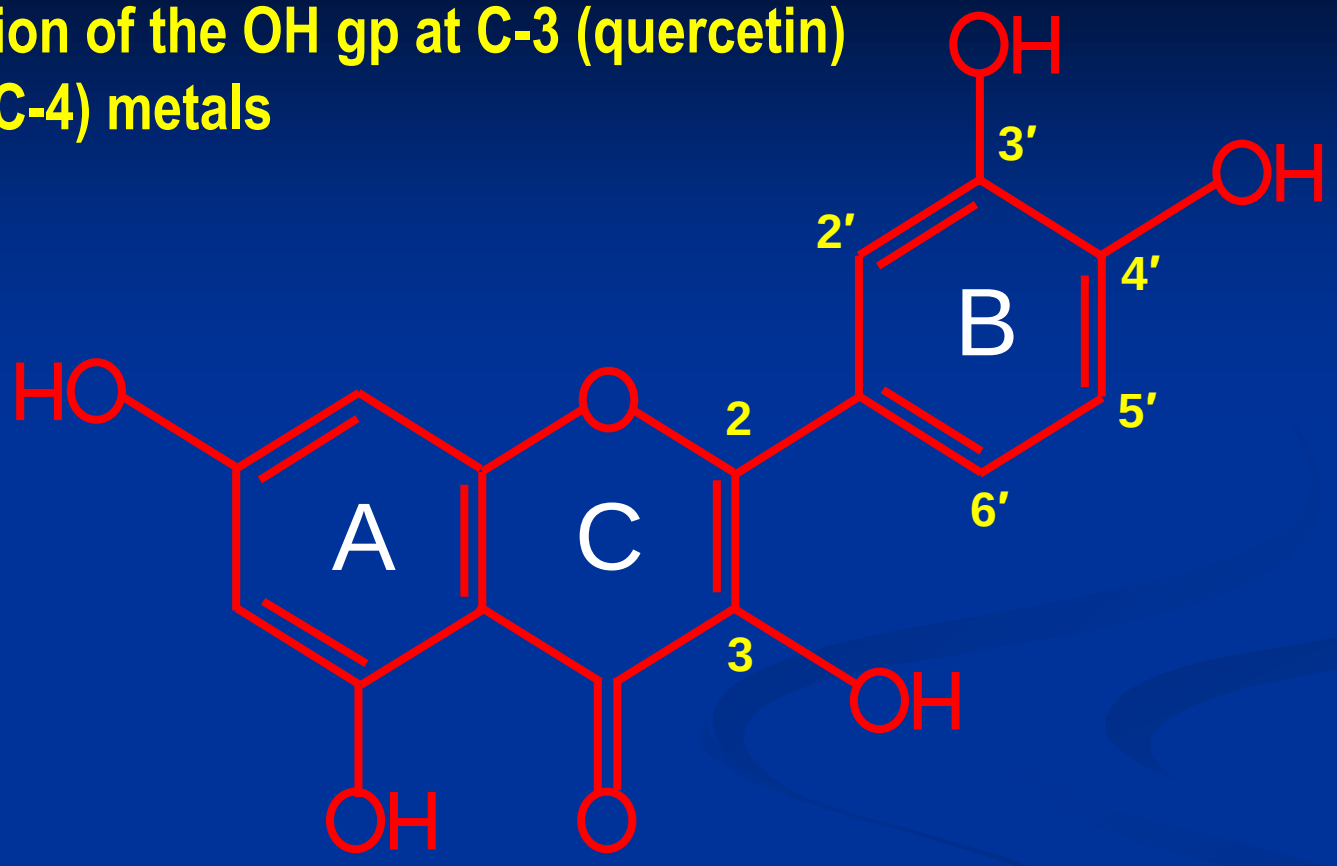
Terpene content of cannabis



Antioxidant Capacity of Flavonoids - Quercetin a Flavonol

Actions: function of the OH gp at C-3 (quercetin)

chelate (C-3 & C-4) metals



The free radicals produced in the body include superoxide and hydroxyl radicals OH• (very reactive). Antioxidants - natural protection from free radicals.

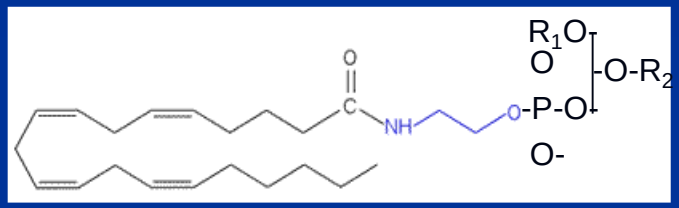
onions and apples rich sources of quercetin

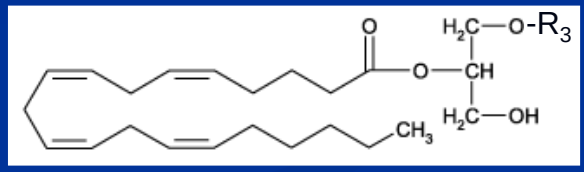
Synthesis and degradation of endocannabinoids endogenous agonists of the cannabinoid receptors - levels influenced by PUFA type and concentrations (n-3 PUFA animal NP)

Are produced as needed
Activate cannabinoid receptors locally
Are immediately metabolized

Phospholipid Remodeling – change arachidonic acid content with NP (n-3 LCPUFA e.g. EPA & DHA)

Phospholipid-derived precursors

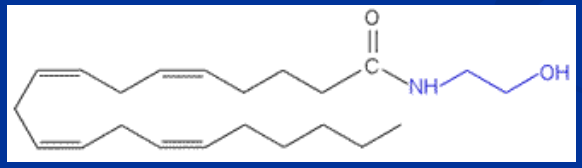


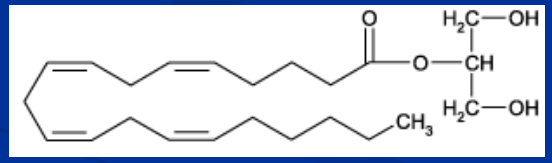


NAPE - PLD

DAG Lipase

Endocannabinoids (Biomol)





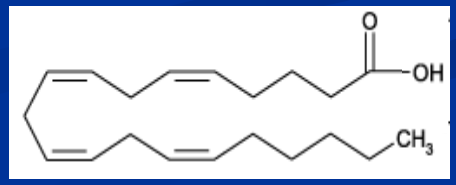
Anandamide (AEA)

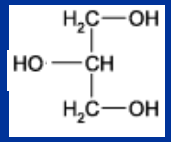
2-Arachidonoylglycerol (2-AG)

Fatty acid amide hydrolase (FAAH)

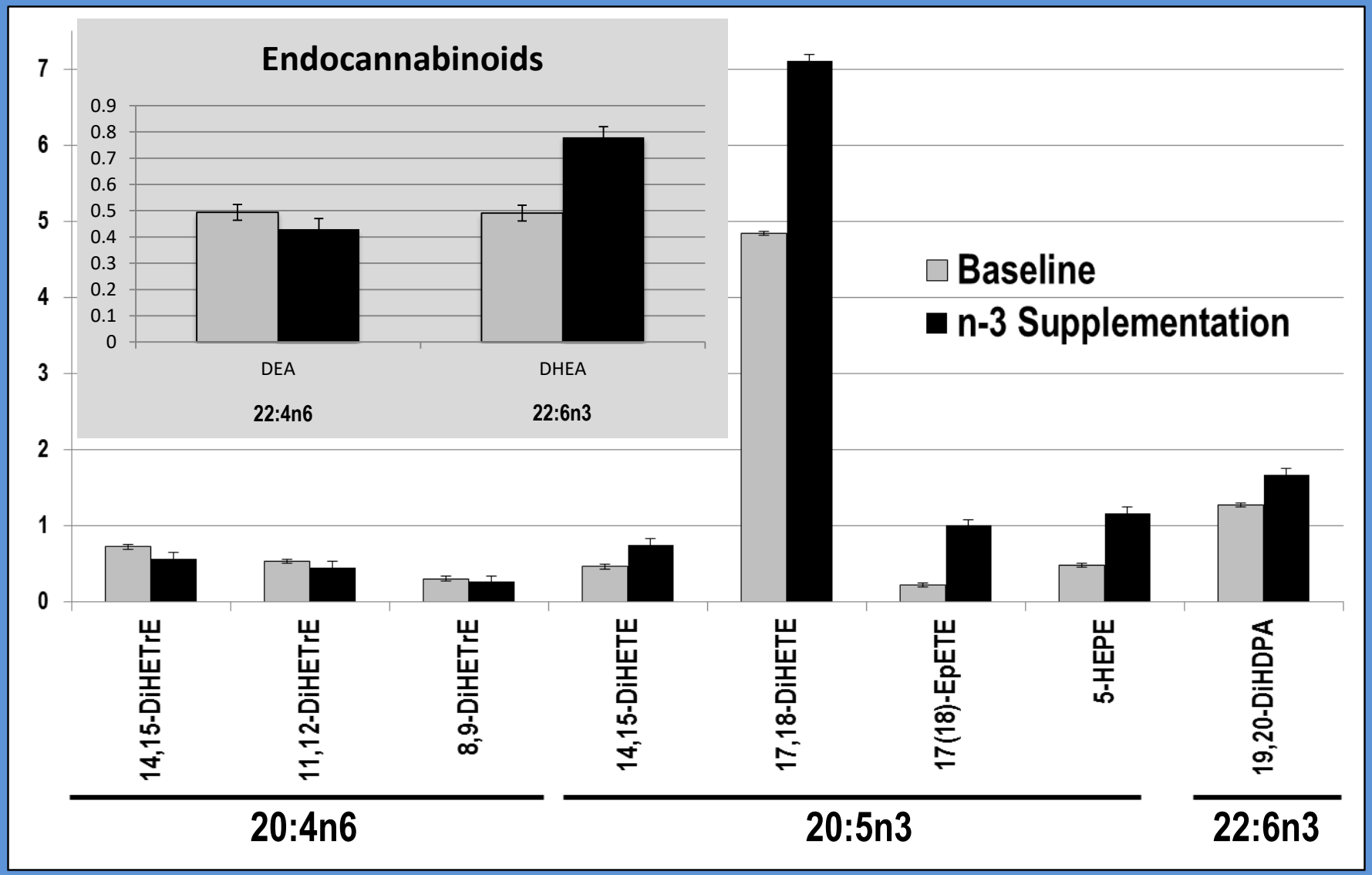
MAG Lipase

Degradation products

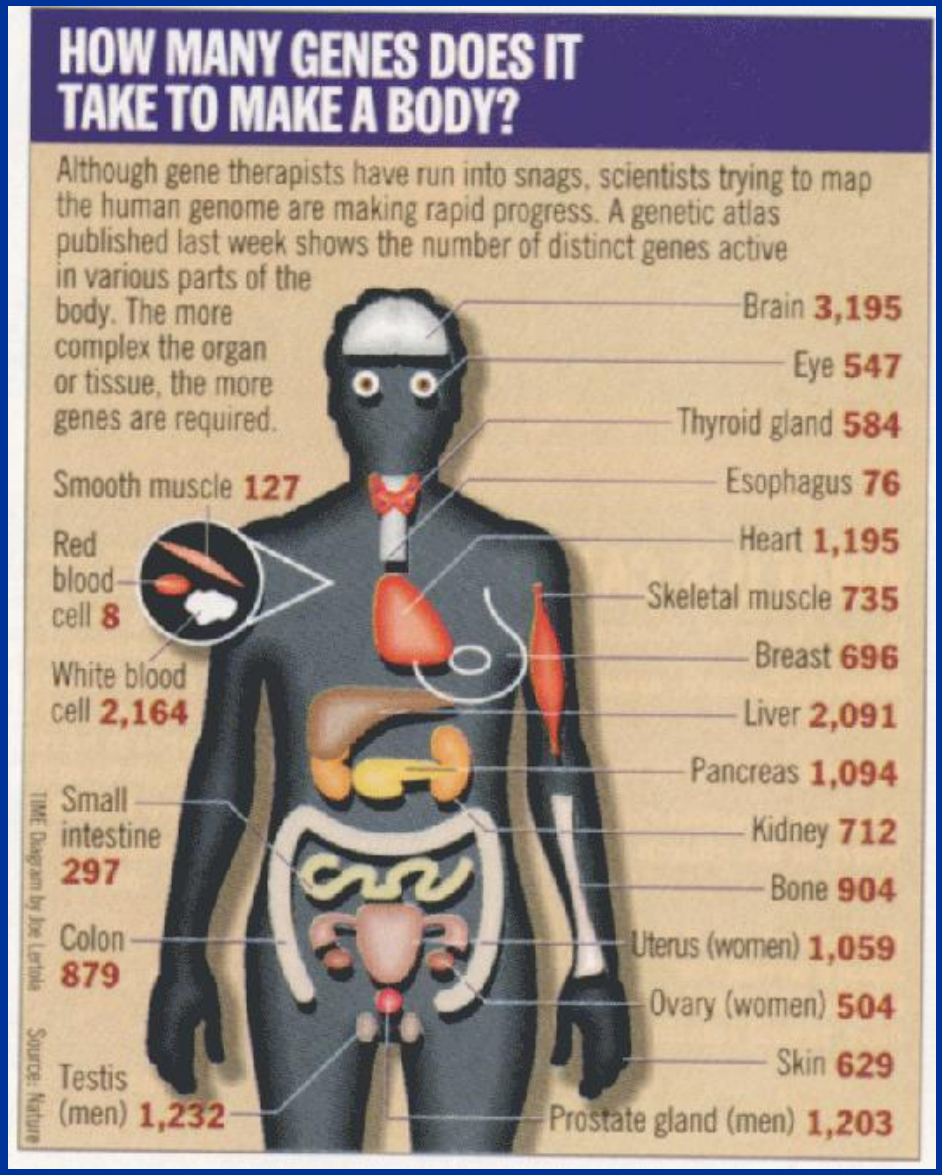




Serum levels of n-3 PUFA-derived oxylipins were higher and n-6-derived oxylipins lower in women (75 yrs) after 6 months of n-3 PUFA supplementation compared to baseline. LOX – lipoxygenase pathway, CYP - cytochrome P450 superfamily, sEH - soluble epoxide hydrolase. (Watkins et al. 2016).



Genes and Phenotype



- The current reckoning in a genetic database called Ensembl estimates that humans have 24,847 genes
- A new study shows that 20 percent of human genes have been patented in the United States, primarily by private firms and universities.

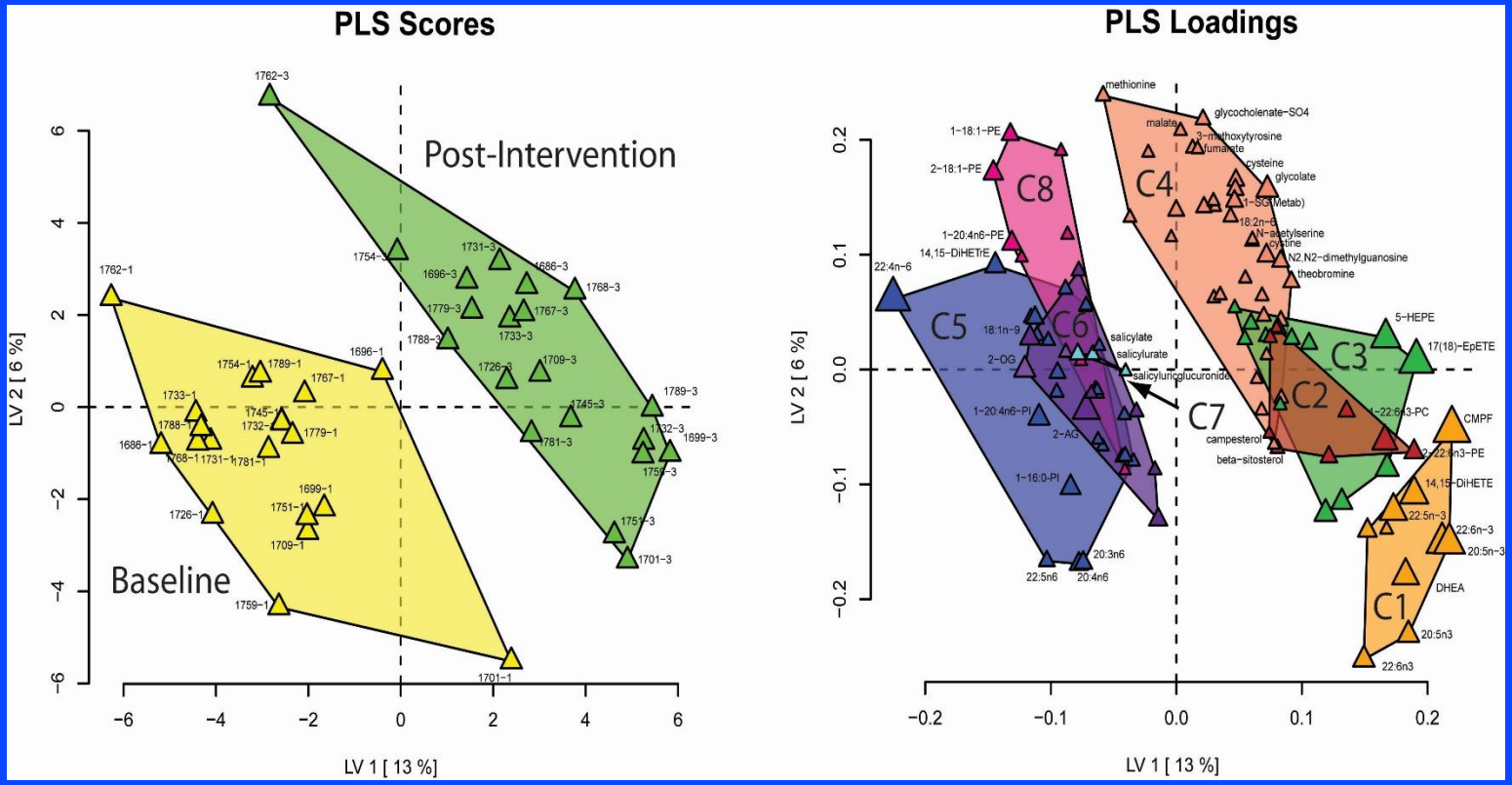
Molecular Targets of NP (Phytochemicals)

The phytochemical NP appear to be important non-nutrient dietary factors that influence gene expression.

- **Direct actions on genes (via transcription factors)**
- **Indirect actions via cell signalling pathways**
- **Indirect actions via metabolites (metabolomics)**

N-3 PUFA supplementation on metabolite profiles in postmenopausal women (Watkins et al., BBA 2016)

PLS scores and PLS Loadings of PMW for changes in *serum metabolites* at baseline in yellow and after 6 months of n-3 PUFA supplementation in green. Partial least squares discriminate analysis of variable importance plot filtered data set (n=109 variables). Eight independent clusters (C1-C8) were produced for values that were **higher** (C1-C4) and **lower** (C5-C-8), N = 20 subjects.



Summary - *Natural products and chronic pain*

- NP molecular aspects
  - Route of administration, absorption, distribution, metabolism, excretion
  - Extracts of plant NP, purity and activity, dose
  - Recognized actions of NP, relation to CNS and peripheral system
- Experimental
  - Animal model matched with target of action, anti-inflammatory and pain, ECS activation, & pro-inflammatory genes
  - Recognize factors that alter NP action, diets used in animal studies
  - Related metabolic/physiologic actions of NP
  - Relationships to cannabinoid receptors, eCB, oxlipins, & cytokines
- Future research
  - Ascertain synergistic actions of NP with drugs used to control pain
  - Molecular targets
  - Metabolomics – metabolite identification

Supplement: Omega-3 PUFA reduce AA and pro-inflammatory COX pathway products (PGE_2)

Membrane Phospholipids

PLA_2 + Inflammation PLA_2

AA EPA

COX-1 COX-2 + Cytokines COX-1 COX-2

PGH_2 PGH_3

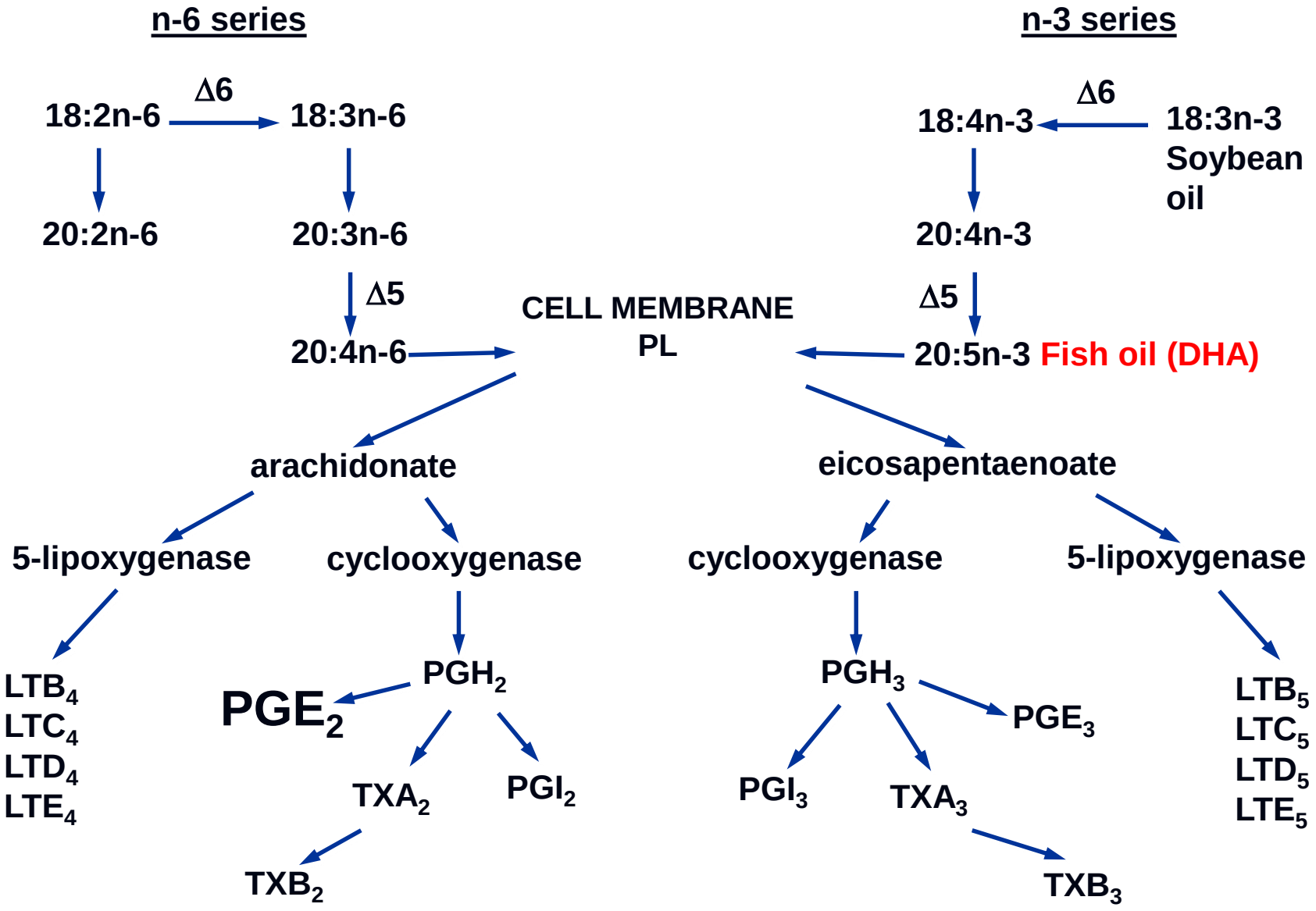
PGE_2 PGI_2 TXA_2 PGE_3 PGI_3 TXA_3

Western diets lead to more PGE_2 production than Asian diets

Diet consumed dictates the prostanoids produced and endocannabinoids

Endocannabinoid system is regulated by AA agonists (EPA/DHA decrease agonists)

Supplement: PUFA formation and phospholipid remodeling: COX & LOX enzymes, oxylipins



Supplemental Materials

Suggested references

Watkins and colleagues:

Association between plasma endocannabinoids and appetite in hemodialysis patients: a pilot study. (2016) *Nutr Res* 36:658-662.

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Supplemental Materials

Suggested references

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