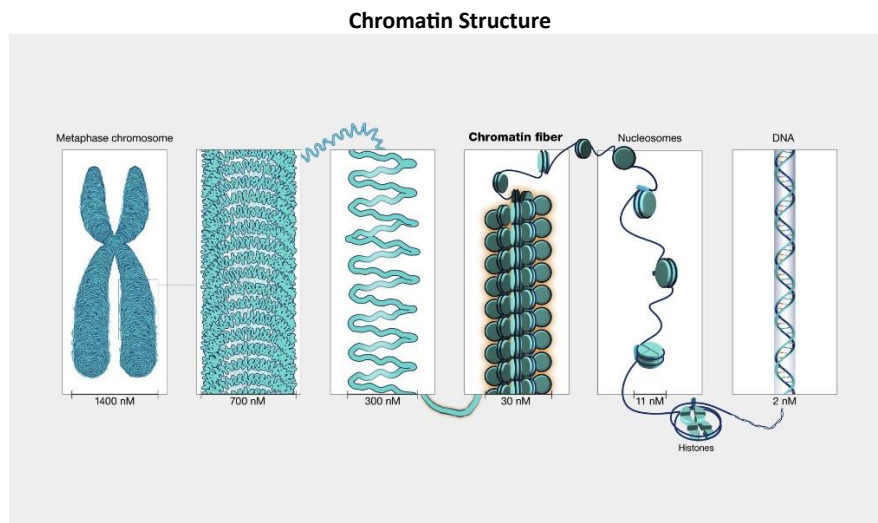


Brain DNA Nerve (Neuronal) and Non-neuronal Cell Methylation

1. What is the importance of methylation in the body and what is it?

- **DNA methylation** is:
 - A biological process that occurs in the addition of essential amino acid methionine-containing methyl group molecules to the DNA molecule.
 - A crucial element in the control of the precise expression of genetic information.
 - A type of an **epigenetic** mechanism essential for normal cell development and stem cell differentiation, or can be associated with aging and various diseased conditions such as the formation of cancers.
- **Epigenetics** is defined as:
 - Somatically heritable states of gene expression (a change to a person's DNA that occurs after conception) due to changes in **chromatin** structure.
 - Examples of epigenetic effects are: **DNA methylation, histone modifications, and chromatin remodeling.**
 - Histone – a protein that provides structural support for a chromosome.
 - Chromatin - DNA and proteins that form the chromosomes.
 - Chromatin remodeling - provide the mechanism for modifying chromatin, allowing transcription signals to reach their destinations on the DNA strand.



- Epigenetic research reveals the mechanisms that contribute to degenerative health conditions such as cancer, inflammation, obesity, insulin resistance, type 2 diabetes mellitus, cardiovascular diseases, neurodegenerative diseases, and immune diseases.
- Induced epigenetic changes can be incorporated or inherited during cell division, becoming a permanent composition of the acquired phenotype, which is the observable characteristics of an individual resulting from the interaction of its genotype (the complete set of DNA) with the environment.

- Epigenetics is vitally important in the nutritional field since **nutrients and other bioactive nutrient factors (phytochemicals and plant cell organelle components)** are able to modify epigenetic actions such as *altering gene expressions*.
 - Folate, vitamin B12, methionine, choline, and betaine have a direct essential effect on DNA and histone methylation.
 - Such bioactive food components direct enzymes that are involved in epigenetic mechanisms that alter gene expression, and can affect physiologic and pathologic conditions in one's lifetime.
 - Genistein and tea catechins activate DNMT enzymes(DNA methyltransferases).
 - Resveratrol, butyrate, sulforaphane diallyl sulfide inhibit HDAC enzymes (histone deacetylases) while curcumin inhibits HAT (histone acetyltransferases) THAT weaken or disrupt interactions between histones and DNA.
 - DNMT actions, affected by bioactive nutrient factors in foods, can change the body's DNA methylation, which in turn affects gene expressions and therefore chromosomal integrity.

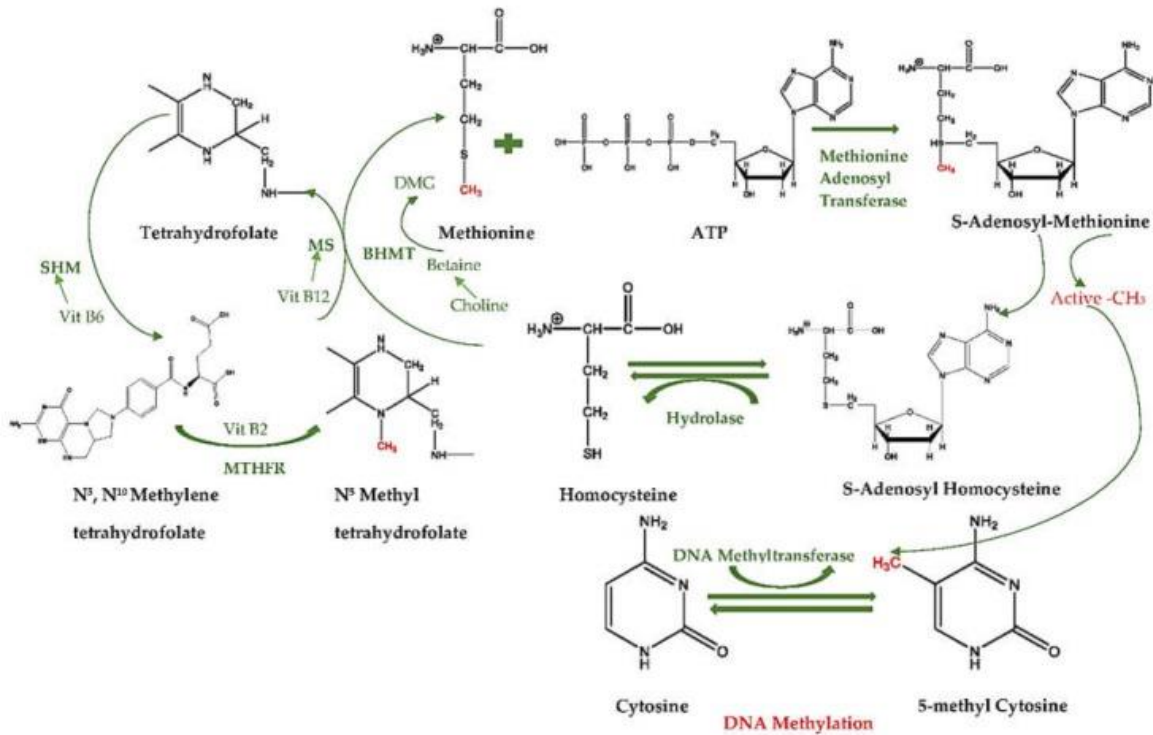
- In autoimmunity conditions after age 50, human T lymphocyte immune cells have shown DNA demethylation and overexpression of genes.
 - Resulting in the switching on of genes in aging cells or cell senescence.
 - Associated with cell degradation of the extra-cellular matrix (ECM) and production of inflammatory proteins such as cytokines that lead to tissue damage.

- **The B vitamin folate** is essential for:
 - DNA methylation during early embryonic period; deficiency in early pregnancy is associated with risk of neural tube defects.

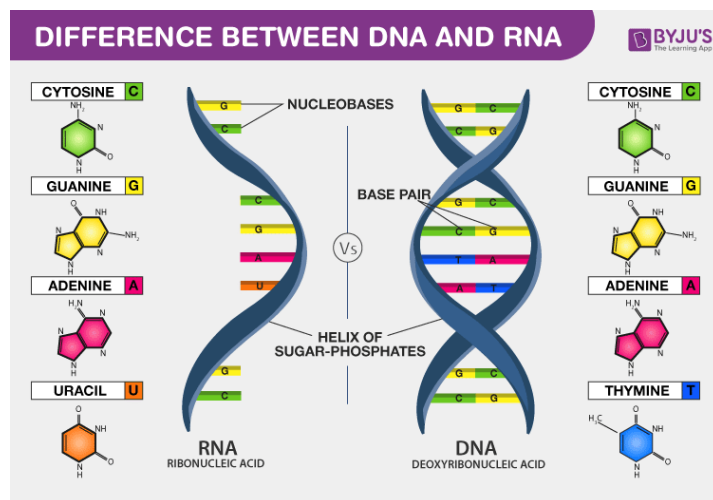
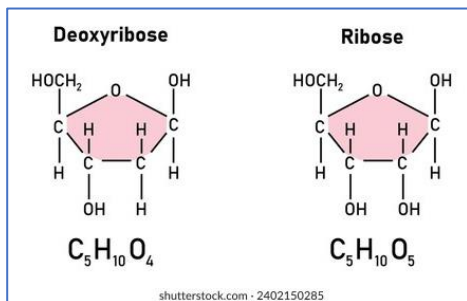
- Deficiency in **choline**, a biochemical that supports nerve, brain and muscle movement, could change DNA methylation during the embryonic period and alter fetal brain development.
 - **Choline is present in ginger root, ginkgo leaf, and *Panax ginseng* root in APLGO's BRN.**

- **Vitamin B-12 (cobalamin)** is essential as a cofactor for the enzyme methionine synthase known to affect genome DNA methylation. (Choi, 2010).

**Various Methyl Groups Influenced by Nutrients for
Generating Amino Acids, Enzymes, Energy Production—All Affecting Genetic Information**

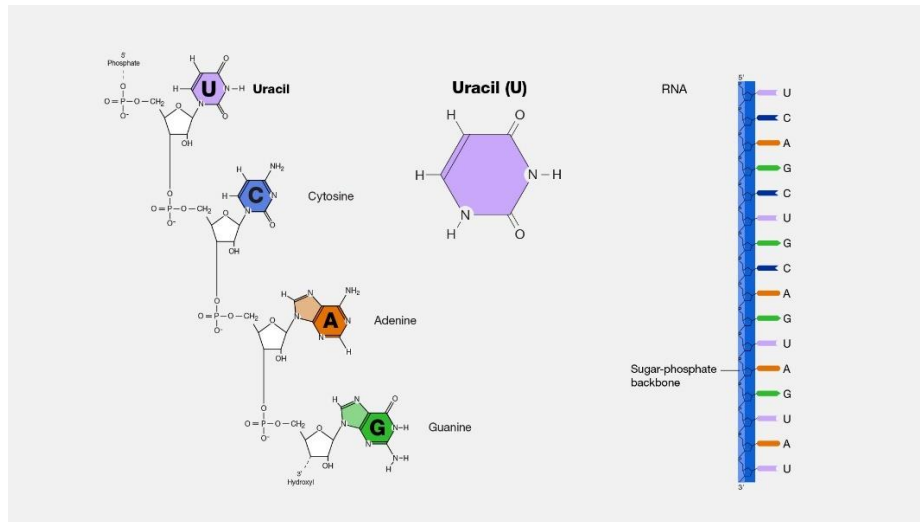


- When present, DNA methylation generally represses or activates **gene expression** or sequence of gene codes on the DNA.
- DNA methylation is a vital modification process in the control of genetic information, a type of epigenetics (*the regulating of gene expressions without changing their sequences in the DNA*), unlike in actual gene mutations.
- The high energy transfer potential of **SAMe (S-adenosyl-l-methionine)** known to restore brain mitochondrial membrane fluidity; SAMe provides the main activated methyl donors for DNA methylation, which is generated by the transference of ATP (the energy molecule) to the sulfur atom of the **essential amino acid methionine**, enabling it to be transferred to various acceptors to be hydrolyzed or split into homocysteine and adenosine.
 - *The body cannot make methionine; it must be obtained from animal-derived, complete protein foods.*
 - *Homocysteine* - an amino acid broken down in the body by the B vitamins B12, B6, and folacin.
 - *Adenosine* – a signaling molecule composed of **adenine**, one of the four bases on the **deoxyribonucleic acid (DNA)**, as well as **ribose sugar**, which forms part of the structural backbone of **ribonucleic acid (RNA)**.



<https://byjus.com/biology/difference-between-dna-and-rna/>

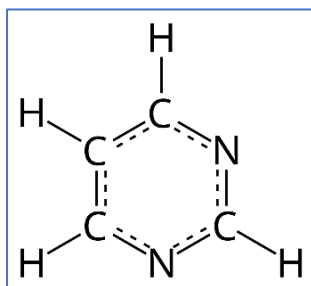
The RNA Molecule



Uracil (U) pairs with adenine (A), and is one of the four nucleotide bases in RNA.
In a DNA molecule, the nucleotide thymine (T) is used in place of uracil.

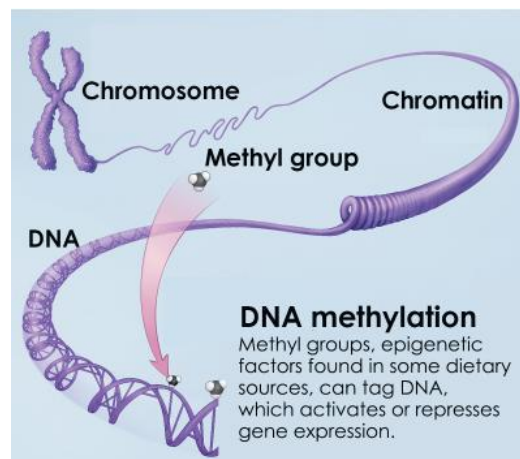
- **Abnormal DNA methylation pathways (hypomethylation and hypermethylation) are the result of improper gene expressions, leading to various health disorders.**
 - Two risk factors that alter epigenetic regulation of methylation pathways: genetic and modifiable factors such as nutrition.
 - **Nutrition is one of the strongest modifiable factors, directly affecting DNA methylation pathways.**
 - Nutrition alters the substrates (substance upon which an enzyme acts) and cofactors (mineral ion required for enzyme catalyst functions) needed for correct DNA methylation.
- DNA methylation regulation pathways have been shown to explain how nutrients function in epigenetics (how behaviors and environments can cause changes that affect how genes function and how the body reads a DNA sequence).
- **DNA methylation pathways are reversible.**
- **Cytosine (C)**, transfers epigenetic information through biochemical modification of its *pyrimidine-nitrogen ring*, and is added to the DNA molecule as a **methyl group** via the Dimethyltransferase (DNMT) enzyme.

Pyrimidine-Nitrogen Ring



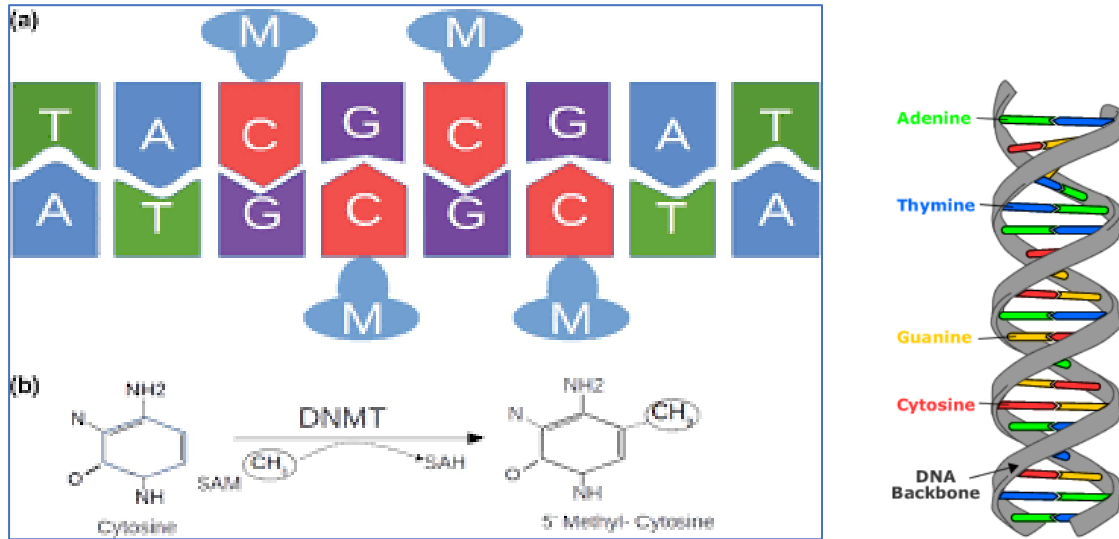
Jynto – 2014, Wikimedia Public Domain

DNA Methylation

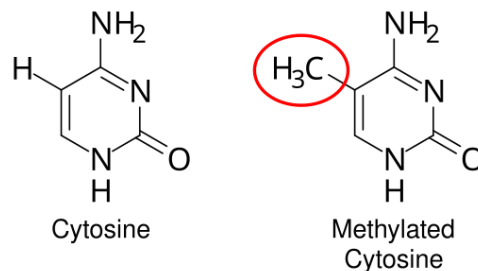


[NIH Common Fund, 2020](#)

**A DNA Methylation, Addition of Methyl Group (-CH₂) to Cytosine on the DNA Molecule
Via Dimethyltransferase Enzyme (DNMT)**



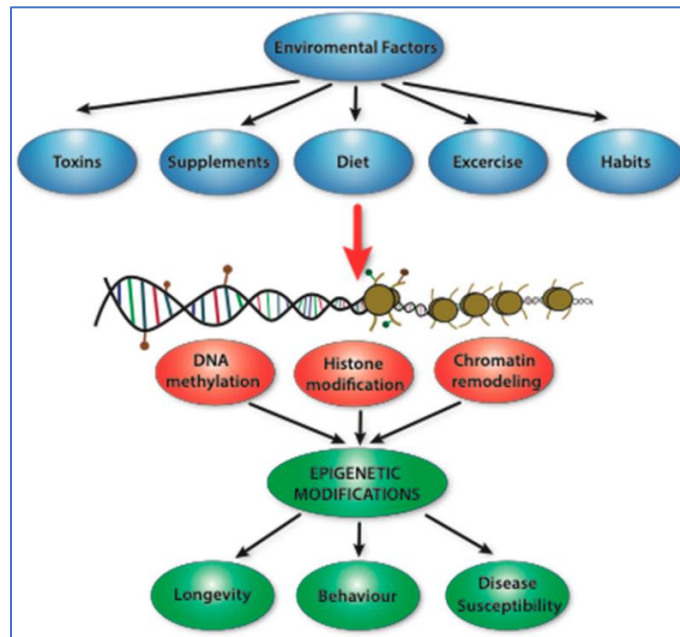
- Methylation of the 5th position (H₃C) of cytosine has an important impact on genome stability, gene expression, and development.



- For methylation, the *essential amino acid methionine* requires B complexes of vitamins Riboflavin (B₂), Pyridoxin (B₆), and Cobalamin (B₁₂), critical precursors for the manufacture of SAME (S-adenosyl-L-methionine), the key methyl donor for DNA and methyltransferase (DNMT) enzymes.
- Diets deficient* in precursors for SAME as a methyl donor and proteins can cause DNA *hypomethylation*; *high-fat diets* also can result in unwanted epigenetic changes in methylation (Kadayifci, 2018).
- Research indicates DNA methylation may be modifiable by *environmental factors* such as physiological and emotional stress, child abuse, nutritional deprivation, nutrient deficiencies.
- With MRI technology, there is an enhanced capacity to understand variations in brain structure and function conferred by the genome, such as genetic traits, disease resistance, and other vulnerabilities.
 - Peer-reviewed studies showed associations between DNA methylation and human brain structure and function.*
 - DNA methylation dysregulation implicated through MRIs shows linking associations with many disorders: genetic neurological and neurodevelopmental disorders, major depression, suicidality, alcohol use, schizophrenia, psychosis, aging stroke, ataxia, neurodegeneration, post-traumatic stress disorder, socio-emotional processing and other problems associated with stress and trauma.

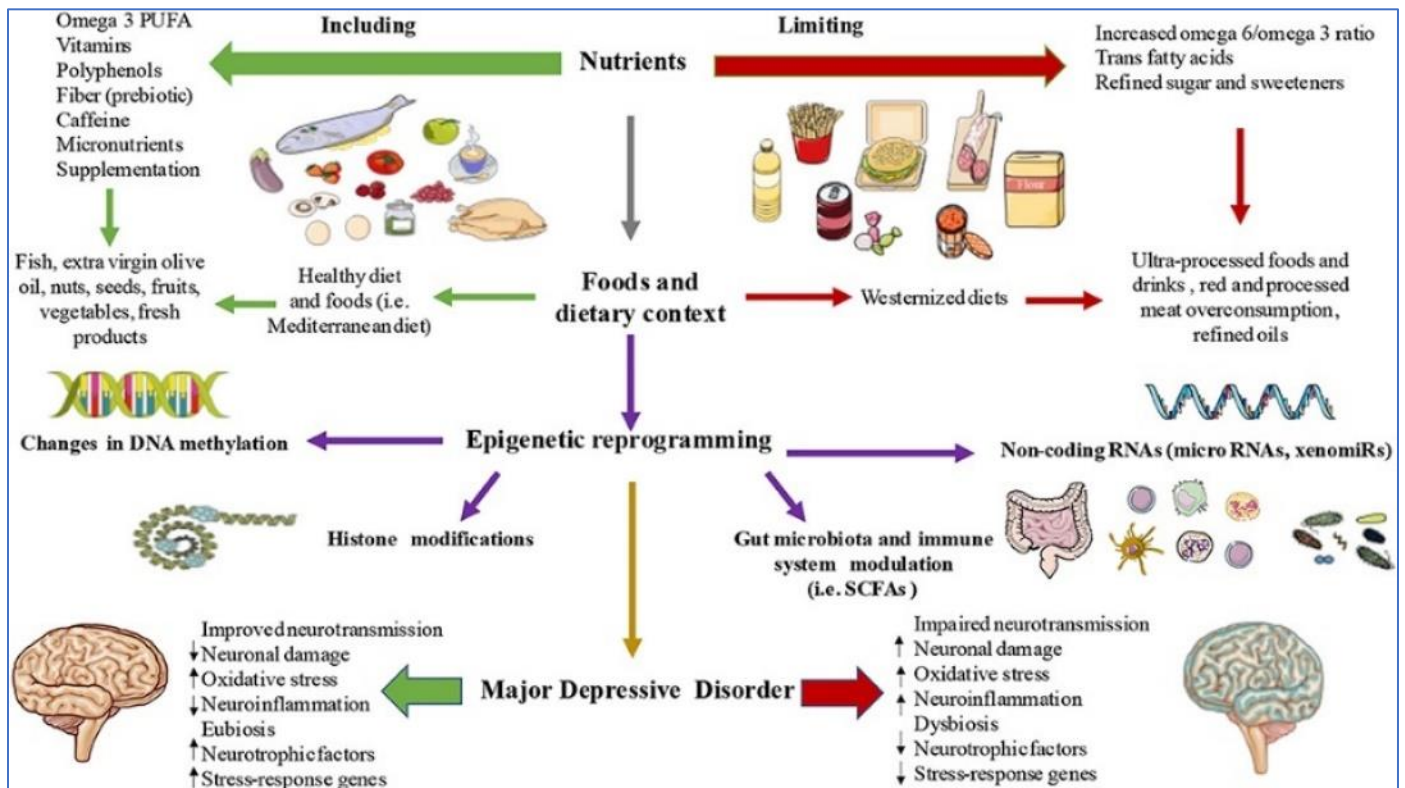
(Wheater, 2020)

The Impact of Essential Nutritional Supplements on DNA Methylation



<https://www.mdpi.com/2072-6643/16/5/678>

Nutrition, Epigenetics, and Methylation – Understanding the Connection



<https://www.frontiersin.org/journals/nutrition/articles/10.3389/fnut.2022.867150/full>

2. Can the APLGO Acumullit SA technology in our lozenges help with methylation triggering in the body?

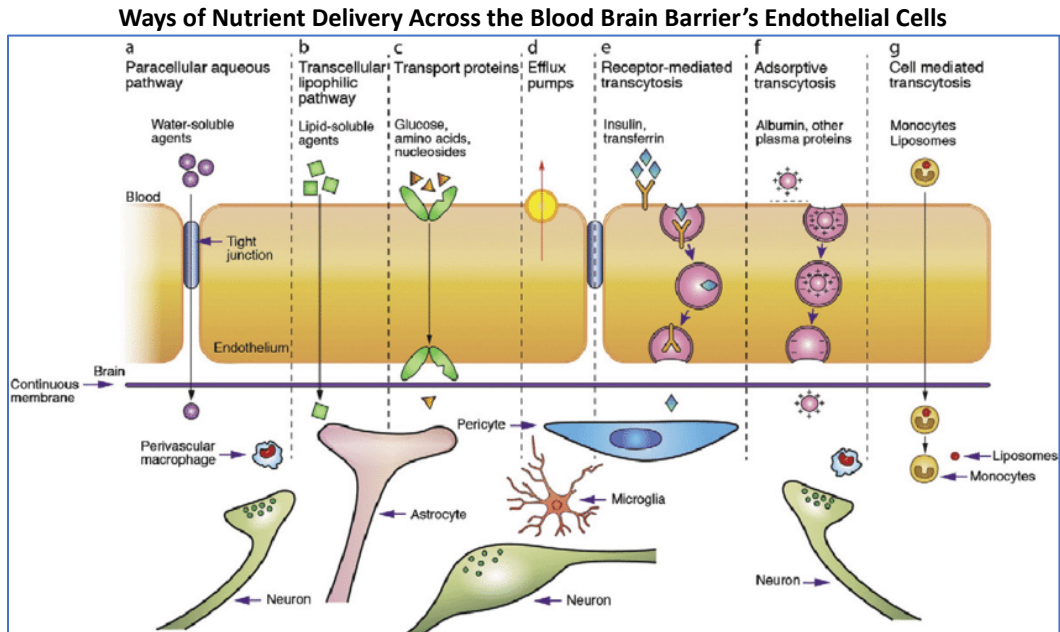
- Due to APLGO'S Acumullit SA technology, the active, viable, negatively charged ions held in the botanical phytonutrient factors in the drops contain the electrical potential or "spark" needed to activate all biochemical molecular processes in the normal cascade effect driving all perpetual actions in the body.
- Those actions involve the ongoing methylation processes having an effect throughout the body, including those occurring in cells of the brain (Gilbert, 2024).

3. What Ingredients in BRN can help with methylation? IE: turmeric, B vitamins, green tea, and ginseng.

- Bioactive phytonutrients (found in the BRN and other drops) *have been shown to help regulate DNA methylation* such as:
 - **Green tea** - epigallocatechin-3-gallate (EGCG), polyphenols catechin and epicatechin, and bioflavonoids genestein, quercetin, fisetin, and myricetin.
 - **Coffee bean** - caffeic acid, an anti-inflammatory polyphenol with free radical neutralizing properties that reduce oxidative stress that can lead to dementia and rapid aging.
 - **Turmeric** – improves brain function by helping it to produce Brain-Derived-Neurotrophic Factor (BDNF), found to be effective in delaying or even reversing many brain and age-related diseases, depression, and preventing the shrinking of the brain's hippocampus, the area of the brain that functions for learning and memory.
 - **Curcumin in turmeric** has been shown to cross the blood-brain barrier and improve the neurodegenerative process of Alzheimer's disease by blocking B-amyloid, the substance that causes plaques that narrow circulatory passages in the brain (Gilbert, 2024).
- Building evidence shows that DNA methylation plays a critical role in brain function: neurogenesis or new nerve cell formation; neuronal differentiation and maturation; synaptogenesis or formation of new synaptic connections; and learning and memory (Xie, 2023).

4. BRN for cognitive thinking and many other issues works so well. Can you explain how it crosses the blood/brain barrier to work so efficiently?

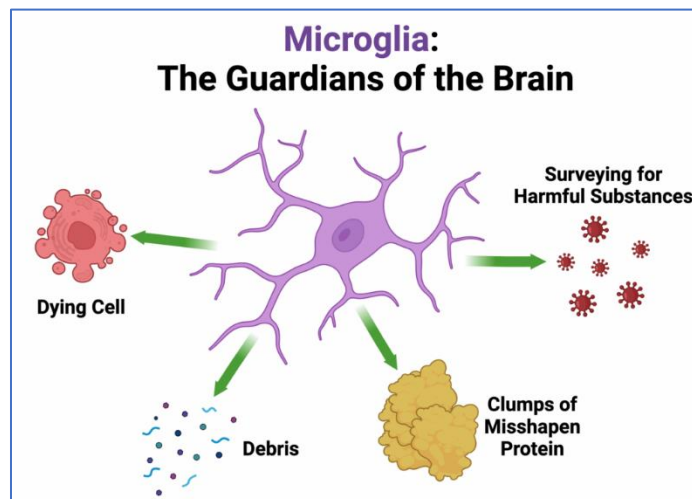
- Blood brain barrier's (BBB) endothelial cells are supported by the direct actions or permeations of neuro-anti-inflammatory, phytochemical plant compounds such as **polyphenols**, which are readily accepted into the brain's inner cell environment, are known to help regulate **microglia** immune cells residing in the brain and spinal cord.



Lihong Liu, 2011.

<https://www.researchgate.net/publication/51864827> Chen Y and Liu L Modern methods for delivery of drugs across the blood-brain barrier *Adv Drug Deliv Rev* 64 640-665.

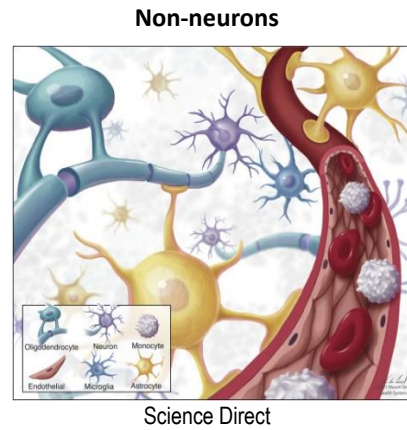
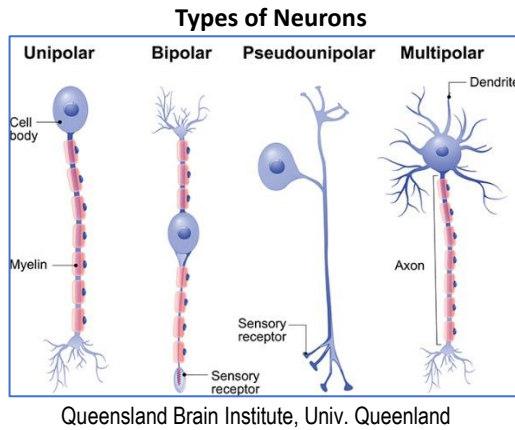
- BRN provides the antioxidant, neuro-anti-inflammatory, phytochemical plant compounds known to prevent neurodegenerative processes through the actions of the **microglia**. (Figueira, 2017)



National Ataxia Foundation

**Research in Brain Region-Specific DNA Methylation
Distinct Cognitive Functions, Behaviors, Development, Metabolic Functions, Inflammatory Responses,
Disorders and Diseases in Epigenetic Landscapes of the Brain**

- Hippocampus – memory
 - Prefrontal cortex – cognition
 - Nucleus accumbens – addictive behavior
 - Distinctions between two types of neurons or nerve cells:
 - Neurons
 - Non-neurons Involved in all aspects of brain function – glial, ependymal, pericytes, progenitor, astrocytes, oligodendrocytes, microglia, epithelial, cells.
- (Rizzardi, 2019) (Argente-Arizón, 2015)



5. Which drop or drops would you recommend taking with BRN to help with methylation?

Polyphenols

- AIR** - amla berry, black currant, cranberry, dog rose, lycium berry (goji, wolf berry)
 - ALT – black currant, green tea leaf
 - BRN** – green tea leaf, magnolia vine fruits, green coffee
 - BTY – green tea leaf, lemon, magnolia vine fruits, pomegranate, strawberry
 - GRW – cranberry, currant, pomegranate
 - GTS – gooseberry, green tea leaf, magnolia vine
 - HPY – passion flower leaf, pear
 - HPR – peach, raisin
 - HRT – mistletoe (white, leaf), pomegranate, raspberry, strawberry
 - ICE – carrot, meadowsweet
 - MLS** – cinnamon bark, cranberry, black currant, sweetie (*Oro blanco*), thyme leaf
 - PFT – brown algae, horseradish, tree leaf
 - PWR Lemon – fig, lemon, pomegranate
 - RLX – passion flower
 - SLD – balsam pear, green tea leaf, strawberry
 - STP – cherry, raspberry
- (Gilbert, 2024)

Flavonoids (Converted to Bioflavonoids in the Body): Genestein, Quercetin, Fisetin, Myricetin

- AIR - amla berry, black currant, cranberry, dog rose, lycium berry (goji, wolf berry)
- ALT - black currant, eucalyptus, grape seed, green tea leaf, licorice root, mangosteen, grape color extract

BRN - apple, asparagus root, damiana leaf, ginkgo, Asian (*Panax*) ginseng root, green tea leaf, magnolia vine fruits, Siberian (*Eleuthero*) ginseng root

BTY – apple, German chamomile flower, Siberian (*Eleuthero*) ginseng root, grape seed, green tea leaf, lemon, licorice root, magnolia vine fruit, milk thistle seed, pomegranate, strawberry

GRW – balsam pear fruit, cranberry, currant, pomegranate, purple coneflower root (*Echinacea*), grape color extract, grape natural flavoring

GTS – apple, Siberian (*Eleuthero*) ginseng root, gooseberry, green tea leaf, magnolia vine fruits, pineapple

HPY – banana, German chamomile flower, ginkgo, hemp seed, licorice root, passion flower leaf, sea buckthorn berry

HPR – milk thistle

HRT – grape seed, hawthorn flower, mistle toe (white, leaf), pomegranate, raspberry, strawberry

ICE – carrot, German chamomile flower, licorice root, meadowsweet leaf, sea buckthorn berry

MLS - German chamomile flower, cinnamon bark, coriander seed, cranberry, black currant, grapefruit, licorice root, mandarin, papaya, purple cornflower root, sweetie (*Oro blanco*), thyme leaf

NRM – apple, balsam pear, Siberian (*Eleuthero*) ginseng root

PFT – barley seeds, brown algae, tomato extract (fruit pulp)

PWR Apricot – apricot, asparagus root, damiana leaf, ginkgo leaf

PWR Lemon, damiana leaf, fig, Asian (*Panax*) ginseng root, lemon, pomegranate seed

RLX – banana, German chamomile flower, Siberian (*Eleuthero*) ginseng root, passion flower leaf

SLD – balsam pear fruit, green tea leaf, licorice root, strawberry

STP – cherry, licorice root, raspberry

(Gilbert, 2024)

Curcuminoids, Including Curcumin, in Turmeric Root

BRN, BTY, HPY, HPR, MLS, PFT, SLD, STP

(Gilbert, 2024)

More on How BRN Botanical Nutrient Factors Protect the Brain, Nervous, and other Body Systems

Apple (*Malus domestica*)

- Quercetin – decreased cerebrovascular conditions, lowered mortality from ischemic (reduced blood flow) heart disease.
- Decreased risk of thrombotic stroke
(Boyer, 2004), (Knekt, 2000)

Ashwagandha Root (*Withania somnifera*)

- Promotes cognition, helps prevent memory deficit and neurodegenerative diseases such as Alzheimer's, Huntington's and Parkinson's diseases.
- Supports formation of new dendrites or neuropathway extensions of nerve cells.
(Gilbert, 2024)

Asparagus Root (*Asparagus racemosus*)

- Contains enzymes that metabolize, neutralize and eliminate the toxic effects of alcohol's ethanol, alcohol dehydrogenase and aldehydes dehydrogenase
- Has a protective effect on liver toxicity as a result of drinking alcoholic beverages.
- Found to suppress certain biomarkers of cell toxicity such as ROS (reactive oxygen species) in liver cancer cells.
- Contains inulin, important digestive support nutrient.
- Contains anti-inflammatory saponins asparaninA, sarsasapogenin, ptotodioscin and diosgenin.
- Contains flavonoids quercetin, rutin, kaempferol and isorhamnetin.
(Gilbert, 2024)

Bilberry (*Vaccinium myrtillus*)

- Contains antioxidant phenolic compounds: quercetin, catechins, tannins, ellagitannins, phenolic acids, and particularly high in anthocyanins.
- Improves cell-signaling pathways in the nervous system, gene expression and repair, stabilization of DNA genetic code, and its antineoplastic effects (helps prevent formation of abnormal tissue growths).
(Gilbert, 2024)

Coffee (*Coffea*)

- Contain caffeine – stimulates production of catecholamines: epinephrine (adrenaline) and norepinephrine (noradrenaline) via the hypothalamus gland and the nervous system.
- Helps mobilize energy quickly to the brain, heart and the muscles, normally in response to social or mental stress or a physical threat in the “fight or flight” response.
(Gilbert, 2024)

Turmeric Root (*Curcuma longa*)

- Helps the brain produce more Brain-Derived-Neurotrophic Factor (BDNF), effective in delaying or reversing brain and age-related diseases and depression.
- Helps prevent shrinking of the brain’s hippocampus, the area of brain functioning for learning and memory.
- Curcumin in turmeric – shown to cross the blood-brain barrier, and to reverse the neurodegenerative process of Alzheimer’s disease by blocking B-amyloid, the substance that causes plaques that narrow circulatory passages in the brain.
(Gilbert, 2024)

Damiana Leaf (*Turnera diffusa*)

- Used in anxiety neurosis associated with depression, nervous dyspepsia.
- Contains twenty-two flavonoids, and monoterpenoids, sesquiterpenoids, triterpenoids, and fatty acids.
- Contains thirty-five phytonutrient antioxidant compounds in these classifications:
 - Terpenoids
 - Saccharides
 - Phenolics
 - Cyanogenic derivatives such as luteolins, apigenins, syringentin and laricitin.
(Gilbert, 2024)

Ginger Root (*Zingiber officinale*)

- High in choline, a neurotransmitter precursor of acetylcholine for nerve, brain, muscle movement functions.
- Prevents fatty liver.
- Contains linoleic acid, a primary essential fatty acid for generating other critical fatty acids for cell membrane maintenance of brain and nervous system.
- Contains oleic acid, a naturally occurring monounsaturated omega-9 fatty acid in humans and animals.
(Gilbert, 2024)

Ginkgo Leaf (*Ginkgo biloba*)

- Shown to be a safe and effective botanical for improving symptoms of Alzheimer’s, vascular dementia (brain damage caused by multiple strokes).
- Shown to improve menopausal disorders: memory, concentration, depression, dizziness, and tinnitus (ringing in the ears).
- Contains phytochemical, antioxidant and anti-inflammatory flavonoids and terpenoids:
 - Flavonoids - found to inactivate the effects of oxygen toxicity.
 - Terpenoids - found to prevent formation of blood clotting factors and protect nerve cells in the brain.
 - Flavonoids and terpenoids together help: improve memory and learning ability and microcirculation; increase hypoxia tolerance in brain cells (ability to tolerate oxygen deficiency, such as the adaptive response in scuba diving); improve blood viscosity or decrease blood’s thickness.

- Are thought to enhance cholinergic processes (the releasing of or responding to acetylcholine, a chemical released by nerve cells that sends signals to other cells) in the brain's hippocampus, the center of the autonomic (involuntary or unconscious) nervous system that influences emotions and spatial working memory.
- Cholinergic transmissions - associated with increased brain electrical activity through improved cerebral blood flow in the brain's visual cortex, the portion of the cerebral cortex that receives and processes impulses from the optic nerves.

(Gilbert, 2024)

Ginseng, Asian, Root (*Panax ginseng*)

- Ginsenosides - stimulatory effect on the brain through the release of chemicals that affect cell-to-cell nerve signaling resulting in improved alertness:
 - Attenuate nerve cell self-destruction (apoptosis) after cerebral tissue injury when blood and oxygen supply return to the injured tissue.
 - Increase uptake of choline, for structuring of cell membranes.
 - Modulate acetylcholine (Ach), a neurotransmitter in cell signaling important for learning and memory.
 - Improve cognitive impairment in learning, remembering, making decisions, learning new things.
 - Improve hippocampus senescence (deterioration due to aging), the part of the brain that regulates emotions and maintains long term memory.

(Gilbert, 2024)

Green Tea Leaf (*Camelia sinensis*)

- Accelerates decomposition of cholesterol and fats in the blood.
- Helps prevent narrowing of blood vessels and hemorrhaging.
- Strengthens blood vessel walls.
- Helps prevent atherosclerosis, and other heart, brain and blood vessel diseases.

(Gilbert, 2024)

Magnolia Vine Fruits (*Schisandra chinensis*)

- Boosts muscle strength, lung capacity, physical and mental performance.
- Used in cases of asthenic (weakness, lack of energy).
- Used in cases of asthenodepressive syndromes of mentally disturbed people and nervous patients.
- Contains a class of unique dibenzo[a,c]cyclooctadiene lignans referred exclusively as "Schisandra lignans": schisandrin, schisandrins B and C., γ-schisandrin, schisantherins A and B, schisanthenol, deoxyschisandrin, gomisins A and G and others being discovered as research in Magnolia vine continues.
- Contains flavonoids: hyperoside, isoquercitrin, rutin and quercetin.

(Gilbert, 2024)

Ginseng, Siberian, Root (*Eleutherococcus senticosus*)

- Contains flavonoids: hyperin, rutin, afzelin, quercetin, kaempferol.
- Contains phenolic acids, triterpenic acids and anthocyanins.
- Found to improve brain activity: protects cognition, improves focus and alertness.
- Anti-inflammatory, neuroprotective.

(Gilbert, 2024)

Water Hyssop Leaf (*Bacopa monnieri*)

- One of the most scientifically studied plants for its actions on brain and nervous system.
- Shown to improve cognitive performance (reasoning, attention, memory, language, attainment of information), and increased choice reaction time.
- Shown to stimulate and maintain nerve and brain cells, enhancing memory.
- Studies show success in treating pain, epilepsy and inflammation.

(Gilbert, 2024)

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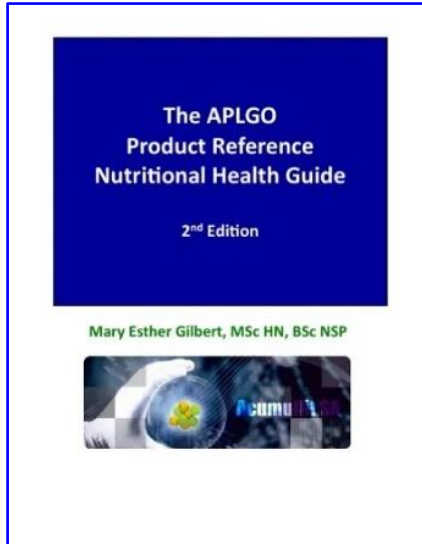
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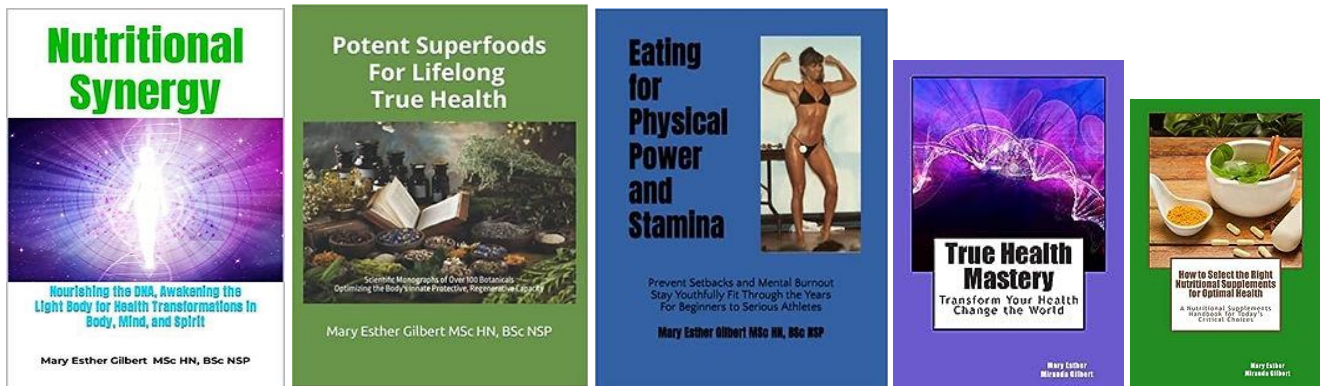
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