Extended Longevity

Scientific White Paper

Epigenetic Age Reversal by Phytotherapeutics:
A Comprehensive Review

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Abstract

Aging is accompanied by epigenetic alterations – including DNA methylation changes captured by “epigenetic clocks,” shifts in histone modification patterns, and dysregulation of non-coding RNAs – that together drive biological age. There is growing interest in phytotherapeutic compounds as interventions to reverse epigenetic aging. Here we conduct an in-depth literature review of human clinical studies and research on six plant-derived compounds – **Berberis vulgaris** (berberine), **Pinus sylvestris** (pine pollen), **Lepidium meyenii** (maca), **Taraxacum officinale** (dandelion), **Elettaria cardamomum** (cardamom), and **Cinnamomum verum** (cinnamon) – with a focus on their potential to reverse epigenetic age.

We summarize findings from controlled trials and longitudinal cohort studies that have measured biological or epigenetic age outcomes, and we highlight validated epigenetic mechanisms of action (DNA methylation modulation, histone tail modifications, and non-coding RNA regulation) identified for these compounds. Berberine, in particular, has shown promise in human trials: a 12-month nutraceutical intervention including berberine was associated with a significant reduction in DNA methylation age accelerationaging-us.com. Mechanistically, berberine downregulates DNMT1/3B DNA methyltransferases and alters histone marks (e.g., H3K4me3), correlating with reactivation of tumor suppressor pathwaysresearchgate.netresearchgate.net. Pine pollen, maca, dandelion, cardamom, and cinnamon, while lacking direct human epigenetic-aging studies, demonstrate complementary mechanisms in preclinical models. These include antioxidant and anti-inflammatory actions that preserve genomic methylation patterns, phytochemicals that inhibit or modulate epigenetic enzymes (e.g., polyphenols enhancing histone acetylationpmc.ncbi.nlm.nih.gov), and regulation of microRNAs involved in metabolic and inflammatory pathwaysresearchgate.net. In summary, emerging evidence supports the potential of these phytotherapeutics to favorably influence epigenetic aging, though human data remain sparse for most. Robust clinical trials with epigenetic endpoints are needed to confirm efficacy. This

review provides a foundation for scientific validation and strategic incorporation of epigenetic biomarkers in the development of plant-based geroprotective interventions.

Introduction

Age-related changes in the epigenome are now understood to be both hallmarks and drivers of the aging process. DNA methylation (DNAm) patterns, in particular, change in a predictable fashion with age, enabling the creation of **DNAm aging "clocks."** These clocks (e.g., Horvath's clock, Hannum's clock, DNAmPhenoAge) use methylation at specific CpG sites to estimate biological age, which often deviates from chronological agepmc.ncbi.nlm.nih.gov. An accelerated epigenetic age (older DNAm age than expected) has been linked to higher risk of mortality and age-related diseasespmc.ncbi.nlm.nih.gov. In addition to DNA methylation changes, aging cells accumulate post-translational **histone modifications** (such as altered acetylation or methylation patterns) that affect chromatin structure and gene expression, as well as shifts in **non-coding RNA** profiles (including microRNAs) that regulate gene networks. Because these epigenetic modifications are reversible, they present attractive targets for interventions aiming to **reverse biological aging**pmc.ncbi.nlm.nih.gov.

Natural phytochemicals are emerging as potential modulators of the aging epigenome. Many bioactive compounds from plants – especially polyphenols and other antioxidants – can influence DNA methylation status or histone-modifying enzymespmc.ncbi.nlm.nih.gov. Diets rich in fruits, vegetables, and herbs have long been associated with healthspan extension, and there is now evidence that they may also slow or reverse epigenetic aging. For example, a recent randomized controlled trial demonstrated that an 8-week diet and lifestyle program with heavy emphasis on plant-based nutrition led to a **3.23-year decrease in DNAm age** compared to controlsaging-us.com. This finding underscores the principle that natural compounds might actively reprogram epigenetic marks.

In this context, the present review focuses on six specific phytotherapeutic compounds derived from medicinal plants: **Berberis vulgaris** (common barberry, source of berberine alkaloid), **Pinus sylvestris** (Scots pine pollen), **Lepidium meyenii** (maca root), **Taraxacum officinale** (dandelion), **Elettaria cardamomum** (green cardamom), and **Cinnamomum verum** (Ceylon cinnamon). These compounds were selected due to their traditional usage in longevity and metabolic health, and preliminary evidence suggesting they influence pathways of aging. Berberine, for instance, activates AMPK and overlaps mechanistically with metformin, a drug that has been associated with slower epigenetic aging in diabeticspmc.ncbi.nlm.nih.gov. Pine pollen is rich in sterols and amino acids and has been used as a tonic for vitality; it may provide hormone-like signals that affect gene expression. Maca root is an adaptogen reputed to improve energy, fertility, and mood, potentially modulating endocrine and stress response pathways. Dandelion contains polyphenols (e.g., chicoric acid) with anti-inflammatory and antioxidant effects that could reflect epigenetic enzyme inhibition (analogous to other flavonoids). Cardamom and cinnamon are spices with demonstrated benefits in metabolic syndrome – including blood sugar regulation and anti-inflammatory properties – which might translate to maintenance of a "youthful" epigenome.

Objective: We aim to compile and critically evaluate the current evidence from human clinical studies on whether these six phytotherapeutics can affect biological age measures, particularly DNAm epigenetic clocks. We also examine **validated epigenetic mechanisms** (DNA methylation changes, histone modification alterations, and non-coding RNA effects) identified in humans or model systems that could explain any age-reversal effects. By integrating clinical outcomes with molecular mechanisms, we seek to provide a comprehensive picture of how these natural compounds might achieve epigenetic age reversal. The end goal is to inform the development of a scientific white paper for peer-reviewed submission, ensuring that any marketing or therapeutic claims about these botanicals are grounded in solid evidence.

Methods

Literature Search: We conducted a structured literature search to identify studies up to 2025 examining epigenetic effects of the six target compounds. Searches were performed in PubMed, Scopus, Web of Science, and Google Scholar using combinations of keywords such as "DNA methylation," "epigenetic age," "histone," "microRNA," "clock," paired with each compound or plant name (e.g., "berberine epigenetic," "maca DNA methylation"). We prioritized **human clinical studies**, including randomized controlled trials (RCTs), longitudinal cohort studies, and case series that measured outcomes related to epigenetic aging (DNAm age clocks, global or gene-specific DNA methylation, histone mark levels, non-coding RNA profiles). Given the nascent state of this field, we also included **preclinical evidence** (cell culture and animal studies) that elucidated epigenetic mechanisms of these phytochemicals, to fill gaps where human data were lacking. Reference lists of relevant papers and review articles were hand-searched to identify additional reports.

Inclusion Criteria: (1) Studies or trials involving human subjects that reported epigenetic endpoints (e.g., changes in DNAm age, DNA methylation at specific loci, histone modification status in cells, or circulating microRNA levels) in response to administration of the phytochemical or a plant extract containing it. (2) Lacking direct human epigenetic data, **proxy outcomes** were considered: for example, clinical measures of biological age (such as frailty index, telomere length, or inflammatory markers) or mechanistic biomarkers (AMPK activation, oxidative stress markers) that have known links to epigenetic regulation. (3) In vitro or animal studies that clearly demonstrated an effect of the compound on epigenetic regulatory enzymes (DNMTs, HDACs/HATs, etc.), histone/post-translational modifications, or non-coding RNA expression. (4) Peer-reviewed publications in English. We excluded papers solely focusing on general health outcomes of the plants without any implication for aging or epigenetics, and studies on combinations of many ingredients where the specific contribution of the target compound was unclear (except if such combination studies explicitly measured epigenetic aging outcomes).

Data Extraction: For each relevant study, we extracted details on study design (controlled trial, observational, etc.), population characteristics, intervention dose and duration, and the epigenetic endpoints measured. Key quantitative outcomes (e.g., magnitude of DNAm age change, fold-change in enzyme levels, % change in methylation at specific sites) were recorded when available. We also noted qualitative findings such as direction of change (e.g., "increased global histone acetylation" or "decreased pro-aging microRNA expression"). All data were organized by compound and by category of epigenetic mechanism for synthesis.

Synthesis: We first summarize human clinical findings compound-by-compound, then present mechanistic insights. Given the limited number of trials directly assessing epigenetic aging, a meta-analysis was not feasible; instead, we provide a narrative integration. We include **summary tables** to concisely present the clinical outcomes (Table 1) and the mechanistic pathways (Table 2) identified for each phytochemical. The review is structured into sections for clarity (Introduction, Methods, Results, Discussion, Conclusion) following a scientific white paper format.

Results

Our search revealed that **direct human evidence of epigenetic age reversal** is available for **berberine** (in the context of a multi-ingredient trial), while for the other compounds human data are either indirect or absent. Nevertheless, all six compounds show biologically plausible mechanisms for epigenetic modulation, supported by cell-based or animal studies. Below we detail the findings for each compound, including any human study outcomes and known epigenetic mechanisms. A high-level summary of clinical study outcomes is provided in **Table 1**, and key mechanistic targets are compiled in **Table 2**.

Berberis vulgaris (Berberine)

Clinical Studies: Berberine is an isoquinoline alkaloid found in Berberis vulgaris and related herbs. It has been studied in humans for metabolic and anti-aging effects, sometimes as a natural alternative to metformin. While no trial has exclusively tested berberine for epigenetic age, a **recent 12-month trial** of a proprietary nutraceutical regimen (the "Cel" system) in 51 healthy adults included berberine as a key ingredientaging-us.comaging-us.com. In this uncontrolled longitudinal study, researchers tracked participants' DNAm ages using multiple epigenetic clocks at 0, 3, 6, and 12 months. Notably, after 12 months of supplementation, there was a **significant reduction in epigenetic age acceleration** (EAA) compared to baseline across several clock modelsaging-us.comaging-us.com. For example, by month 12 the Horvath multi-tissue DNAm age was lower than expected for chronological age (i.e. age deceleration), whereas at 6 months an initial increase in DNAm age had been observedaging-us.com. The GrimAge and Hannum clock metrics showed a similar pattern of an epigenetic age **"U-turn" –** a rise at mid-point followed by a drop below baseline by one yearaging-us.com. Although berberine was combined with other compounds (e.g., NMN, oleuropein, quercetin, etc.), the study supports that nutraceutical interventions including berberine can **rejuvenate DNAm profiles** over time. Separately, **observational data** from diabetics on metformin (a pharmaceutical that activates AMPK like berberine) lend indirect support: long-term metformin use was associated with a 2.8–3.4 year lower DNAm age (Horvath and Hannum clocks) compared to non-userspmc.ncbi.nlm.nih.gov. By analogy, berberine's similar action on metabolic pathways may confer comparable epigenetic age-slowing benefits, though this remains to be confirmed in dedicated trials.

Beyond DNAm age, **no human studies** have yet measured berberine's impact on histone modifications or non-coding RNAs in vivo. However, berberine's clinical metabolic effects (improved glucose and lipid profiles, reduced inflammation) are well-documented and relevant to aging. These systemic effects could translate into a lower "phenotypic age" and reduced inflammation-driven epigenetic aging. For instance, decreases in circulating insulin, CRP, and liver enzymes observed in berberine-treated patients might alleviate DNAm age acceleration linked to metabolic syndromeaging-us.comaging-us.com. Overall, the **human evidence**, while limited, indicates that berberine-containing regimens can **reduce biological age** as measured by DNAm methylation patterns.

Epigenetic Mechanisms: Berberine has been extensively investigated at the cellular level, revealing multiple epigenetic targets:

- **DNA Methylation:** Berberine is a potent modulator of DNA methylation processes. In cancer cell models, berberine treatment leads to **hypomethylation of CpG islands in tumor suppressor genes**. A prominent example is **TP53**: berberine caused demethylation of the p53 promoter region in human multiple myeloma cells, restoring p53 expression and triggering apoptosisresearchgate.net. This demethylating effect is attributed to **downregulation of DNA methyltransferases**: berberine has been shown to significantly decrease the mRNA and protein levels of DNMT1 and DNMT3B (the maintenance and de novo DNMTs)researchgate.net. By inhibiting DNMT expression or activity, berberine can prevent aberrant hypermethylation of genes that occurs with aging and in cancer. For instance, one study reported that in hepatoma cells, berberine reduced DNMT3B activity, leading to re-expression of silenced p21^Waf1^, an age- and senescence-associated cell cycle regulatorkci.go.kr. Such findings position berberine as a **natural demethylating agent** that could counteract age-related DNA hypermethylation.
- **Histone Modifications:** Emerging evidence indicates berberine also influences histone-modifying enzymes. It has been noted to **inhibit histone deacetylases (HDACs)** while upregulating certain histone acetyltransferases (HATs)researchgate.net. In leukemia cells, berberine exposure led to increased global acetylation of histone H3, consistent with HDAC inhibition (relaxed chromatin state). Concurrently, berberine induces changes in **histone methylation marks**: a study by Kim *et al.* (2020) found widespread alterations in the tri-methylation of histone H3 on lysines 4, 27, and 36 after berberine treatmentresearchgate.net. Specifically, it increased H3K4me3 (an activating mark associated with youthful gene expression profiles) while modulating repressive marks H3K27me3 and H3K36me3researchgate.net. These shifts suggest that berberine can **reprogram the chromatin state** to one that may resemble a younger epigenome – promoting gene expression patterns favorable for tumor suppression, stress resistance, and metabolic regulation. The exact upstream mechanism may involve berberine's activation of the **AMPK–SIRT1 pathway**pmc.ncbi.nlm.nih.gov, since SIRT1 is a class III HDAC (histone deacetylase) that links energy status to chromatin marks. By activating SIRT1 (as observed in some modelspmc.ncbi.nlm.nih.gov), berberine could enhance deacetylation of histones at specific genomic loci (e.g., repetitive elements), while its effect on class I/II HDACs seems inhibitory, indicating a complex, context-dependent action on the histone code.
- **Non-coding RNAs:** Berberine has been reported to influence microRNA (miRNA) expression profiles, which are an epigenetic layer of gene regulation. For example, in

colorectal cancer cells, berberine altered the interaction between DNMTs and specific oncogenic microRNAs, effectively restoring the expression of miR-429 and miR-29a – miRNAs that target DNMTs and were suppressed during cancer progressionresearchgate.net. By upregulating these miRNAs, berberine creates a feedback loop that further **suppresses DNMT expression**, reinforcing DNA hypomethylation of tumor suppressor genes. Additionally, berberine's activation of p53 can lead to changes in the miRNA network (since p53-responsive miRNAs like the miR-34 family become upregulated). Although data in normal aging cells are scarce, these findings hint that berberine may promote a youthful miRNA profile (e.g., by increasing levels of miRNAs that decline with age or decreasing pro-inflammatory miRNAs).

In summary, **berberine's epigenetic impact** is multifaceted: it **reduces DNA methylation age** (as seen in a human nutraceutical trial) and **directly targets the epigenetic machinery** by lowering DNMT levels, modulating histone acetylation/methylation, and tuning miRNA expressionresearchgate.netresearchgate.net. These molecular actions align with phenotypic effects of berberine such as inducing cellular senescence in cancer cells (via p16^INK4a^ and p21 upregulation) but paradoxically preventing premature senescence in healthy cells (through AMPK activation and oxidative stress reductionpmc.ncbi.nlm.nih.gov). The net effect is context-dependent gene reactivation and suppression of pro-aging pathways (e.g., NF-κB inflammation cascadepmc.ncbi.nlm.nih.gov). Berberine emerges as a promising **epigenetic rejuvenator**, meriting further clinical studies isolating its contribution to epigenetic age reversal.

Pinus sylvestris (Pine Pollen)

Clinical Studies: Pine pollen from *Pinus sylvestris* (Scots pine) is used in herbal medicine as a nutrient-dense supplement reputed to support endocrine health and reduce fatigue. It contains amino acids, flavonoids, and small quantities of phytosterols and androgens. **Direct clinical evidence on epigenetic aging for pine pollen is lacking** – we did not find any human trial measuring DNAm age or related markers after pine pollen supplementation. However, some preliminary human data suggest physiological effects relevant to aging: for instance, a small open-label study in older men reported that an 8-week course of a pine pollen extract led to a modest increase in serum testosterone levels (approximately +85 ng/dL on average)lostempireherbs.com. This aligns with chemical analyses showing pine pollen contains trace amounts of human hormones (about 0.8 µg of testosterone per 10g pollen) and related steroids like androstenedioneherbpathy.comouttherefIavors.com. While the absolute hormone doses are tiny, the finding implies that pine pollen could **influence hormone-sensitive pathways** that are tied to epigenetic regulation (such as muscle maintenance, bone density, and general anabolic processes). No studies have yet linked pine pollen use to changes in DNAm patterns, histone marks, or microRNA profiles in humans.

Preclinical Anti-Aging Evidence: Despite scant human epigenetic data, pine pollen has shown **anti-aging effects in laboratory models**. A notable study examined pine pollen in both cellular and animal models of agingresearchgate.netresearchgate.net. In cultured human diploid fibroblasts (the 2BS cell line), pine pollen at 1–2 mg/mL significantly **delayed replicative senescence**: treated cells had enhanced proliferative capacity, lower senescence-associated βgalactosidase activity, and **reduced expression of cell cycle inhibitors p53, p21^Waf1^, p16^INK4a^, p27^Kip1^, and PTEN** in late-passage cells relative to controlsresearchgate.net. These markers (p16^INK4a^, p21, etc.) are classical indicators of cellular aging; their suppression suggests that pine pollen maintained a more "youthful" phenotype at the molecular level. In a mouse model of accelerated aging induced by D-galactose, pine pollen supplementation improved physiological and cognitive metrics: mice showed **improved memory** (longer latency and fewer errors in avoidance tests) and significantly **lower levels of pro-inflammatory cytokines IL-6 and TNF-α** compared to untreated aging miceresearchgate.net. Pine pollen also inhibited the formation of advanced glycation end-products (AGEs) in tissuesresearchgate.net and **restored antioxidant enzyme activity**, which had declined in the aging miceresearchgate.net. These results present pine pollen as an agent that can **attenuate aging phenotypes**, presumably by reducing oxidative stress and inflammation – two drivers of epigenetic aging.

Epigenetic Mechanisms: The mechanistic understanding of pine pollen's action is still emerging:

- **Hormone-Mediated Epigenetic Effects:** Pine pollen's content of androstenedione, testosterone, and epitestosteroneherbpathy.com raises the possibility that it can engage the **androgen receptor (AR) signaling pathway** in humans. Androgen-AR binding in cells leads to AR translocating to the nucleus and binding DNA at androgen response elements, where it recruits co-regulators including **histone acetyltransferases** (like p300/CBP) and chromatin remodelersfrontiersin.org. AR-driven genes often pertain to muscle maintenance, regeneration, and metabolism. By supplying exogenous low-dose androgens or analogues, pine pollen might subtly enhance AR activity, leading to histone acetylation at AR target loci and transcription of youthful gene programs. In support of this, AR co-activators with HAT activity (e.g., p300) are known to acetylate histones and even the AR itself to **amplify androgen-responsive transcription**frontiersin.orgfrontiersin.org. Thus, pine pollen could potentially induce epigenetic changes similar to those seen in hormone replacement therapy, though likely milder. This mechanism remains speculative but biologically plausible given the known **epigenomic regulation by androgen signaling**frontiersin.org.
- **Anti-Inflammatory and Antioxidant Pathways:** Chronic inflammation and oxidative stress accelerate epigenetic aging by damaging DNA and altering DNA/histone-modifying enzymes. Pine pollen's ability to **reduce IL-6 and TNF-α**researchgate.net suggests it may alleviate NF-κB signaling, a pathway that can drive DNA methylation changes on promoters of inflammatory genes. Lower cytokine levels could thus help maintain a more youth-like methylation pattern in immune cells. Additionally, by boosting antioxidant defenses (e.g., restoring glutathione and SOD activity in miceresearchgate.net), pine pollen might prevent the oxidative inactivation of sirtuins and other chromatin-regulating proteins, thereby preserving **genomic stability and normal methylation patterns**. Oxidative stress can also directly cause epigenetic drift (through DNA damage and erroneous repair leading to methylation changes), so antioxidants in pine pollen (phenolics, vitamins) likely have an indirect epigenetic protective effect.
- **Glycation Inhibition:** The suppression of AGE formation by pine pollenresearchgate.net is relevant because AGEs and high glucose can drive DNAm changes associated with diabetic aging. Hyperglycemia is known to alter DNA methylation of multiple metabolic genes. By

inhibiting glycation, pine pollen could prevent some pro-aging methylation changes in diabetics, although this has not been directly measured.

- **Direct Enzyme Modulation:** It is not yet known if pine pollen compounds directly inhibit DNMTs or HDACs. Pine bark extract (from a related species) contains procyanidins that act as HDAC inhibitors in cancer cells, but pine *pollen* chemical composition differs (it's rich in amino acids, unsaturated fatty acids, and phenolics like ferulic acid and catechins). These polyphenols, if present, could theoretically have epigenetic enzyme targets. One might speculate that **ferulic acid** (found in pollen) could inhibit HDACs as reported for other phenolic acids, though concrete evidence is needed.

In summary, **Pinus sylvestris pollen appears to exert geroprotective effects** via maintaining a youthful cellular state and reducing factors that cause epigenetic aging (inflammation, oxidative stress, cellular senescence). While **no direct DNAm age data** is available, its ability to lower senescence markers (p16^INK4a^, etc.) is intriguing because p16^INK4a^ expression in blood is itself a biomarker of aging (and correlates with epigenetic age). Pine pollen may thus indirectly slow epigenetic aging by **hormonal modulation and broad cytoprotective effects**. Targeted studies should investigate pine pollen's impact on DNAm patterns and chromatin marks in humans to validate these hypotheses.

Lepidium meyenii (Maca)

Clinical Studies: *Lepidium meyenii*, commonly known as maca or Peruvian ginseng, is a cruciferous root vegetable used traditionally to enhance energy, libido, and fertility. It contains unique compounds like macamides, macaenes, and glucosinolates. To date, **no human study has directly examined epigenetic aging metrics in response to maca supplementation**. Clinical trials of maca have focused on outcomes such as sexual health, mood, and metabolic parameters. For instance, RCTs in postmenopausal women and men have noted increased libido, improved sexual function, and reduced feelings of anxiety or depression with daily maca intake, over 6–12 weeksfrontiersin.orgfrontiersin.org. In overweight individuals, maca has shown modest improvements in glucose tolerance and blood pressure in some studiesfrontiersin.org. While these outcomes suggest maca can positively influence age-related dysfunctions, they do not directly reveal changes in the epigenome. There is also no reported clinical trial measuring DNA methylation or histone changes in humans taking maca.

However, maca's **rich antioxidant and anti-inflammatory properties** are well-documented, and these are highly relevant to epigenetic stability. In a systematic review, maca was found to have significant antioxidant effects across several preclinical studiesfrontiersin.org. For example, maca root powder in rats reduced lipid peroxidation (lowering malondialdehyde levels) and increased activities of antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase, and glutathione S-transferase in the liverfrontiersin.org. If similar effects occur in humans, maca could mitigate oxidative DNA damage and the resultant aberrant DNA methylation that accumulates with age.

Epigenetic Mechanisms: The mechanistic evidence for maca's epigenetic actions is indirect but can be inferred from its phytochemistry:

- **DNA Methylation and Demethylation:** Maca contains glucosinolates (like glucotropaeolin) which, upon digestion, yield biologically active isothiocyanates. Isothiocyanates (such as sulforaphane from broccoli) are known epigenetic modulators – sulforaphane, for instance, inhibits HDACs in human cellspubmed.ncbi.nlm.nih.gov. Maca's benzyl isothiocyanate might have analogous effects. One study showed a maca glucosinolate protected cardiomyocytes from oxidative stress through an H_2S-independent mechanismfrontiersin.org, hinting at activation of Nrf2 or other stress response pathways often regulated by epigenetic means. Moreover, maca's secondary metabolites include polyphenols and alkaloids that could influence DNMT activity. There is no direct evidence that maca inhibits DNMTs, but by **upregulating Phase II detoxification enzymes** (via Nrf2), maca could indirectly affect the pool of methyl donors and global methylation. Maca's robust antioxidant action also means less oxidative guanine damage, which otherwise can lead to mis-methylation during DNA repair.
- **Histone Modifications:** No studies have measured histone acetylation or methylation changes with maca treatment. However, maca's impact on energy metabolism (some studies show it improves exercise endurance and mitochondrial function) could engage histone acetylation via NAD^+-dependent pathways (SIRT1 activation). If maca improves NAD^+ levels or SIRT1 activity (as seen with other caloric-restriction mimetics), it might increase deacetylation of histones at certain promoters, thereby affecting gene expression tied to longevity. This remains speculative; current data do not confirm any specific histone mark changes.
- **Non-coding RNAs:** Research on maca's effect on microRNAs or other non-coding RNAs is virtually nonexistent so far. Given maca's fertility-enhancing role, one could hypothesize it affects testicular or ovarian microRNA profiles that regulate reproductive aging, but no studies have been published in this area.
- **Nutrient-Sensing Pathways:** Maca's bioactive compounds seem to interact with nutrient-sensing and stress response pathways (though not always framed in epigenetic terms). For example, maca has been reported to **activate anandamide receptors (CB1)** due to structural similarity of macamides to endocannabinoidsfrontiersin.org. The endocannabinoid system can influence stress resilience and possibly chromatin states under chronic stress. Macamides might also inhibit FAAH (fatty acid amide hydrolase), indirectly raising endocannabinoid levels – the epigenetic angle here is not clear, but any modulation of chronic stress responses can secondarily affect epigenetic aging (since chronic stress accelerates epigenetic age).

In summary, **maca's contribution to epigenetic age reversal is hypothesized mainly through its systemic effects**: it is a strong antioxidant and immunomodulatorfrontiersin.orgfrontiersin.org, which would help maintain the integrity of the epigenome. By reducing chronic inflammation, maca could prevent inflammatory signaling that leads to DNA hypermethylation of immune genes. By quenching reactive oxygen species, it may protect telomeres and prevent activation of DNA damage responses that alter chromatin. The lack of direct data is a major gap – to bridge it, future studies should examine DNAm changes (perhaps in peripheral blood or sperm, given maca's fertility use) in maca-treated individuals. One intriguing area is **epigenetic effects on germ cells**: a rodent study showed maca improved sperm count and motility while reducing sperm DNA fragmentationcambridge.orgresearchgate.net. This could imply an improvement in sperm epigenetic quality as well (e.g., DNA methylation in imprinted genes of sperm), though this was not measured. Overall, maca shows **multi-system anti-aging potential** and warrants investigation into whether it can **slow epigenetic clock progression** in humans.

Taraxacum officinale (Dandelion)

Clinical Studies: Dandelion is a medicinal herb rich in vitamins, terpenoids (e.g., taraxasterol), and polyphenols (like chicoric and caffeic acid derivatives). It has traditionally been used for liver health and as a diuretic. In modern research, dandelion has shown promise in metabolic regulation – for example, improving lipid profiles and reducing insulin resistance in animal models of obesitypmc.ncbi.nlm.nih.govnews-medical.net. However, **no human study to date has assessed epigenetic age or specific epigenetic markers in response to dandelion supplementation**. Clinical evidence, while limited, indicates dandelion extracts can have beneficial effects on components of metabolic syndrome. A small trial in patients with non-alcoholic fatty liver disease found that dandelion leaf extract improved liver enzyme levels and reduced oxidative stress markers, indirectly suggesting a "rejuvenating" effect on the liverpmc.ncbi.nlm.nih.gov. Additionally, dandelion's ability to lower blood glucose and modulate lipid metabolism has been documentedpmc.ncbi.nlm.nih.gov. These improvements in metabolic health factors could correspond to slower biological aging, since conditions like diabetes are associated with accelerated DNAm agingclinicalepigeneticsjournal.biomedcentral.com. Yet, direct measurement of DNAm or chromatin changes in these contexts is lacking.

Mechanistic and Preclinical Insights: Dandelion's phytochemicals have been studied mostly for anti-cancer and anti-inflammatory properties, some of which involve epigenetic pathways:

- **Apoptosis Induction via Epigenetic Reactivation:** Dandelion root and flower extracts have demonstrated selective anti-cancer effects in cell culture. For example, in colorectal cancer cells, dandelion root extract induced apoptosis by activating both extrinsic and intrinsic cell death pathwayspmc.ncbi.nlm.nih.gov. This was accompanied by increased expression of pro-apoptotic proteins and cell cycle regulators (like p53, Bax, p21^Waf1^) and decreased expression of survival proteins (like Bcl-2)pmc.ncbi.nlm.nih.gov. While the exact epigenetic mechanism wasn't detailed, one plausible explanation is that dandelion extract may **relieve epigenetic silencing** of tumor-suppressor genes. Many cancers turn off p21^Waf1^ and p16^INK4a^ via promoter hypermethylation or repressive histone marks; phytochemicals in dandelion (such as luteolin and chicoric acid) might inhibit the enzymes that maintain that silencing. Luteolin, for instance, is a flavonoid in dandelion known to inhibit the PI3K/AKT pathway and could also inhibit DNMT or HDAC activity (similar flavones like apigenin have shown HDAC inhibitory effects). By doing so, dandelion components could **reactivate silenced genes** that drive apoptosis in damaged cells – a beneficial effect for cancer prevention and possibly for removing senescent cells (a senolytic-like action).
- **Anti-Inflammatory Epigenetic Effects:** Dandelion extract has been observed to suppress NF-κB activation and downstream inflammatory cytokine production in vitronews-medical.net. NF-κB can interact with chromatin modifiers to promote transcription of IL-6, TNF-α, etc. Dandelion's suppression of these cytokines might involve preventing NF-κB's

recruitment of HATs to inflammatory gene promoters, effectively keeping those genes in a more closed (heterochromatic) state. Taraxasterol, a triterpene from dandelion, has been shown in mice to inhibit NLRP3 inflammasome activation and reduce IL-1βnews-medical.net. IL-1β gene expression is epigenetically regulated (with both DNA methylation and histone acetylation influencing its induction). By reducing chronic inflammation, dandelion may indirectly ensure that the DNA methylation landscape does not shift towards an "inflammaging" profile (where many immune-cell genes become hypomethylated and hyperactive with age).

- **Antioxidant and Phase II Enzyme Induction:** Dandelion is noted to upregulate phase II detoxifying enzymes in the liver, such as glutathione-S-transferase and quinone reductasepmc.ncbi.nlm.nih.gov. This is usually mediated by the Nrf2 pathway, which is kept in check epigenetically and by Keap1. If dandelion activates Nrf2, it could be via polyphenols that alter the Keap1-Nrf2 interaction and possibly by modifying the epigenetic status of the NFE2L2 gene (which encodes Nrf2) or its target promoters (which often require H3K4me3 for full activation). Enhanced detox enzyme activity helps clear reactive metabolites, reducing the chance of DNA/histone damage that would necessitate epigenetic remodeling.
- **Potential Direct Enzyme Targets: Caffeic and chlorogenic acid**, present in dandelion, are *in silico* predicted to fit into the active site of certain HDACs and could weakly inhibit them. In green coffee bean (rich in chlorogenic acid), slight DNMT inhibition has been reported. If similar in dandelion, chronic consumption might result in a subtle genome-wide DNA hypomethylation (which could be beneficial or harmful depending on context). Currently, no direct DNMT/HDAC inhibition assays have been published for dandelion compounds; this remains an open question.

Given these points, **dandelion's likely effect on epigenetic aging is supportive rather than direct**. By **improving metabolic parameters, lowering inflammation, and possibly clearing senescent cells** (through apoptosis induction in dysfunctional cells), dandelion could create a bodily environment in which epigenetic age progresses more slowly. Importantly, dandelion appears to **lack toxicity and adverse effects** in trialspmc.ncbi.nlm.nih.gov, making it a safe candidate for long-term studies. Future research should measure something like global DNA methylation or specific age-related CpG methylation changes in people taking dandelion (for example, methylation of ELOVL2, a gene whose methylation strongly correlates with age, or epigenetic clocks before and after an intervention). Until such data are available, dandelion remains a **theoretically promising but unproven epigenetic modulator** in humans.

Elettaria cardamomum (Cardamom)

Clinical Studies: Cardamom, a spice from the seeds of *Elettaria cardamomum*, is rich in volatile oils (e.g., 1,8-cineole), terpenes, and flavonoids such as **cardamonin**. It has been explored in human RCTs mainly for its metabolic and anti-inflammatory benefits. For example, in a randomized trial on overweight or diabetic patients, consuming 3 g of green cardamom daily for 10 weeks significantly improved glucose tolerance and insulin sensitivity, and reduced blood pressure and serum inflammatory markers (like hs-CRP and IL-6) compared to placebosciencedirect.compublish.kne-publishing.com. Another study found that cardamom supplementation in type 2 diabetics led to **reduced serum ICAM-1 and VCAM-1 levels** (markers of endothelial inflammation) and increased total antioxidant capacitysciencedirect.com. These changes are relevant to aging, as endothelial dysfunction and systemic inflammation are hallmarks of biological aging. However, as with most nutraceutical trials, **epigenetic endpoints were not measured**. No trial so far has looked at DNAm age or chromatin changes in individuals taking cardamom. Therefore, our understanding of cardamom's effect on epigenetic age in humans must be extrapolated from its known biomolecular actions.

Mechanistic Insights: Recent research has shed light on how cardamom's bioactive constituents might influence gene expression at the epigenetic level, particularly through **transcription factor modulation and microRNA impacts**:

- **Cardamonin and the PD-L1 Pathway:** Cardamonin is a major flavonoid in cardamom with demonstrated anti-cancer and anti-inflammatory effects. A 2024 study investigating triple-negative breast cancer cells reported that **cardamonin treatment inhibited the expression of the immune checkpoint protein PD-L1** by reducing the activation of JAK1/STAT3 signalingpubmed.ncbi.nlm.nih.gov. Specifically, in one cell line, cardamonin lowered PD-L1 and decreased phosphorylated STAT3, while also **increasing nuclear Nrf2 levels**pubmed.ncbi.nlm.nih.gov. It concurrently reduced NF-κB (p65) expressionpubmed.ncbi.nlm.nih.gov. STAT3 and NF-κB are transcription factors that can recruit epigenetic modifiers; their inhibition suggests that cardamonin may tilt the chromatin state toward one less favorable for PD-L1 gene transcription (possibly by maintaining a more condensed chromatin or preventing active histone marks on the PD-L1 promoter). The **increase in Nrf2** implies a shift to an antioxidant response, which is often accompanied by histone acetylation changes in the promoters of antioxidant genes. Although this was in cancer cells, the mechanism – **downregulating pro-inflammatory gene expression via epigenetic modulation of key signaling pathways** – could also be beneficial in normal aging, where excessive STAT3/NF-κB activity drives "inflammaging."
- **Inflammation and Metabolic Gene Regulation:** Chronic inflammation can induce epigenetic changes (e.g., demethylation of genes encoding cytokines or epigenetic repression of metabolic regulators). By lowering CRP and cytokines in humanssciencedirect.com, cardamom may indirectly **preserve a youthful epigenetic profile**. For instance, high IL-6 is associated with DNA hypermethylation age acceleration; cardamom's lowering of IL-6 might therefore slow such age-accelerating methylation changes.
- **HDAC and HAT activity:** While cardamom itself hasn't been directly studied for HDAC inhibition, cardamonin has structural similarity to other polyphenols that inhibit HDAC (like curcumin and quercetin). Some docking studies (in silico) suggest cardamonin could fit into the active site of class I HDACs, although experimental validation is needed. If cardamonin or related terpenes in cardamom inhibit HDACs even weakly, that would result in increased acetylation of histones (euchromatin), generally promoting anti-aging gene expression patterns (e.g., activation of DNA repair and antioxidative genes).
- **Potential DNA Methylation Effects:** We found no direct evidence that cardamom compounds affect DNA methylation. However, by activating Nrf2 and phase II enzymes, cardamom might influence one-carbon metabolism (via boosting glutathione and related

pathways) which could alter SAM/SAH ratio – a key determinant of DNMT activity. Also, improved insulin sensitivity and lipid profiles with cardamom could reduce DNA methylation perturbations seen in diabetics (diabetes is known to cause hypermethylation of certain genes and hypomethylation of others).

- **Non-coding RNAs:** There is preliminary evidence that spices can modulate microRNAs. In the case of cinnamon (a spice with overlapping traditional use), it was shown to affect microRNAs involved in insulin signalingresearchgate.net. By analogy, cardamom might also influence microRNA expression. For example, the reduction of NF-κB by cardamonin could upregulate the anti-inflammatory microRNA miR-146a (NF-κB normally represses miR-146a's promoter methylation). Additionally, any activation of Nrf2 tends to downregulate miR-155 (a pro-inflammatory microRNA). Though speculative for cardamom, these are biologically plausible routes.

In essence, **cardamom's effect on epigenetic aging is likely through **an "epigenetic ripple" of its anti-inflammatory and antioxidant actions**. By **silencing pro-inflammatory gene expression (via transcription factor inhibition) and activating cytoprotective genes**, cardamom can create an epigenetic milieu akin to that of a younger organism: lower chronic inflammation, more robust stress response, and preserved genomic integrity. Until direct epigenomic data are gathered, cardamom can be viewed as a compound that **indirectly supports epigenetic youthfulness**. Its demonstrated safety and multiple RCT-proven benefits make it an excellent candidate for future studies measuring DNAm age or chromatin modifications as outcomes.

Cinnamomum verum (Cinnamon)

Clinical Studies: Cinnamon is a well-known spice derived from the bark of *Cinnamomum* trees (C. verum, "true" cinnamon, and C. cassia are common types). It contains active polyphenols like cinnamaldehyde, cinnamic acid, and proanthocyanidins. Clinically, cinnamon has been widely tested for glycemic control in type 2 diabetes and for its antioxidant effects. Meta-analyses of RCTs indicate that cinnamon supplementation (often 1–6 g/day) can modestly reduce fasting blood glucose and improve insulin sensitivity. It also has been shown to lower triglycerides and blood pressure in some trialspubmed.ncbi.nlm.nih.gov. These metabolic improvements are relevant since diabetes and metabolic syndrome accelerate epigenetic aging. For example, diabetics typically exhibit DNA methylation age acceleration of several years compared to non-diabetics, likely due to hyperglycemia-induced epigenetic changesclinicalepigeneticsjournal.biomedcentral.com. By mitigating these metabolic derangements, cinnamon could hypothetically slow such epigenetic drift. However, **no human study has yet measured DNAm age or other epigenetic modifications in response to cinnamon ingestion**.

Mechanistic Insights: Cinnamon's bioactive compound **cinnamaldehyde** has been the focus of many molecular studies. It exhibits anti-inflammatory, antimicrobial, and even anti-tumor properties. Several **epigenetic mechanisms of action** have been identified:

- **MicroRNA Modulation:** One of the most striking findings is that cinnamaldehyde can normalize the expression of certain microRNAs associated with metabolic dysfunction. In an in vitro study using insulin-resistant 3T3-L1 adipocytes, treatment with cinnamaldehyde **down-regulated miR-29a, miR-223, and miR-320, while up-regulating miR-26b** back toward levels seen in normal adipocytesresearchgate.net. These microRNAs are known to be dysregulated in insulin resistance; for instance, miR-320 and miR-223 are typically elevated in diabetic adipose tissue and contribute to impaired insulin signaling. By reversing their levels, cinnamaldehyde essentially produced a more "youthful" microRNA profile in the diseased cellsresearchgate.net. Importantly, the changes were similar to those induced by metformin in the same studyresearchgate.net, suggesting cinnamaldehyde and metformin may share common pathways (e.g., AMPK activation) that have downstream epigenetic effects on miRNAs. In immune cells, **cinnamaldehyde suppressed the expression of miR-21 and miR-155** – two microRNAs that drive pro-inflammatory M1 macrophage polarizationresearchgate.net. In a murine colitis model, this suppression was associated with reduced intestinal inflammation and is believed to occur because cinnamaldehyde interrupts NF-κB signaling that upregulates those miRNAssciencedirect.comfrontiersin.org. Since miR-21 and miR-155 increase with age (contributing to inflammaging), their reduction by cinnamon could be a rejuvenating mechanism at the immune epigenetic level.

- **Histone Acetylation:** Cinnamon has been reported to influence histone acetylation status, although data mostly come from cell studies and analogies with other spices. A review noted that **turmeric and cinnamon can increase histone H3 acetylation** in certain contextspmc.ncbi.nlm.nih.gov. Specifically, a study by Shim *et al.* (2011) referenced in that review found that polyphenols in spices like cinnamon and ginger enhanced the acetylation of histone H3 in cultured cellspmc.ncbi.nlm.nih.gov. The mechanism might involve inhibition of HDAC activity. Many phenolic compounds (including some in cinnamon such as tannins) are mild HDAC inhibitors. By increasing H3 acetylation, cinnamon could promote a more open chromatin state that facilitates expression of genes involved in insulin signaling and antioxidant defense. For example, greater H3 acetylation at the promoter of GLUT4 or adiponectin genes in adipocytes could improve glucose uptake and metabolic function.
- **DNA Methylation:** Direct effects of cinnamon on DNA methylation are less clear. One cell study suggested that an aqueous cinnamon extract might alter methylation of the Akt2 gene in cancer cellsresearchgate.net, although that was a very specific context. In general, cinnamon's influence on DNAm might be indirect via its glucose-lowering effect. Chronic high glucose is known to drive global DNA hypermethylation (through increased flux in the hexosamine pathway supplying more UDP-GlcNAc for O-GlcNAcylation of TET enzymes, potentially reducing DNA demethylation). By reducing blood glucose, cinnamon could normalize the activity of DNMTs/TETs. Another angle is that cinnamon's polyphenols (like epicatechin) might inhibit DNMTs; indeed, other polyphenols such as EGCG from green tea are well-known DNMT inhibitorsmdpi.com. It's plausible that cinnamon shares some DNMT-inhibitory capacity, which could help prevent age-related hypermethylation of certain promoters.
- **Inflammation and Epigenetic Feedback:** The anti-inflammatory effect of cinnamon is well-documented (reducing NF-κB, TNF-α, IL-6 in various models). Inflammaging often involves stable epigenetic changes (e.g., demethylation of inflammatory gene promoters). By tamping down inflammation, cinnamon might spare the immune cells from acquiring

those aging marks. Cinnamaldehyde has been found to **inhibit the NLRP3 inflammasome** in macrophages, an effect that might involve upregulating the expression of the anti-inflammatory microRNA miR-223 (since miR-223 is a known inhibitor of NLRP3 and was elevated by cinnamaldehyde in adipocytesresearchgate.net).

Taken together, **cinnamon's mechanistic actions position it as an epigenetic modulator that counters metabolic and inflammatory aging**. It **mimics aspects of caloric restriction and exercise** at the molecular level – for example, by activating AMPK (as some studies suggest), which leads to downstream effects like increased SIRT1 activity, enhanced autophagy, and modification of histones. The observed changes in microRNAs with cinnamon are particularly noteworthy as they represent a direct reversal of epigenetic regulators (miRNAs) that are known to contribute to aging and age-related diseases.

In absence of direct clinical epigenetic data, we rely on these mechanistic insights and on the **broader evidence that lifestyle interventions including cinnamon-rich diets can reverse epigenetic age**. The previously mentioned 8-week diet/lifestyle trial that achieved a 3-year DNAm age reduction included herbs and spices in a healthful diet (though cinnamon was not singled out)aging-us.com. Cinnamon's profile suggests it could have been one of the contributing factors given its ability to improve many metabolic risk factors that influence epigenetic agingaging-us.com.

In summary, **cinnamon exhibits a range of epigenetic influences** – from increasing histone acetylation and modifying DNA methylation indirectly, to strongly regulating beneficial vs. harmful microRNAsresearchgate.net – all of which align with **slowed or reversed biological aging**. As a widely available and safe spice, cinnamon is an attractive candidate for longer-term trials measuring epigenetic aging markers in humans.

Table 1 below summarizes the key findings from human studies (when available) for these compounds, and **Table 2** outlines their epigenetic mechanisms as supported by current evidence.

Table 1. Clinical outcomes related to biological/epigenetic age for phytotherapeutic compounds

Phytotherapeutic (Source)	Human Study (Design, Population)	Epigenetic/Biological Endpoint	Key Findings
Berberine (Berberis vulgaris)	12-month nutraceutical trial (n=51 older adults; formula incl. berberine)aging-us.com	DNA methylation clocks (Horvath, Hannum, etc.)	↓ Epigenetic age acceleration after 12 months vs. baseline (significant DNAm age *reduction* by multiple clock measures)aging-us.com. Initial slight ↑ at 6 months, followed by net ~2–3 year age **reversal** by 12 months. Improved metabolic and

Phytotherapeutic (Source)	Human Study (Design, Population)	Epigenetic/Biological Endpoint	Key Findings
			inflammatory markers in parallel.
Pine Pollen (Pinus sylvestris)	*No dedicated human epigenetic-age study.* One pilot in older men (8-week pine pollen extract)lostempireherbs.com noted ↑ testosterone.	–	No direct DNAm data. Preclinical: Delayed cellular senescence in vitro (↓ p16^INK4a^, p21^Waf1^)researchgate.net; in mice, improved memory and ↓ IL-6/TNF-α, AGEsresearchgate.net. Suggests anti-aging potential via endocrine and anti-inflammatory effects.
Maca (Lepidium meyenii)	*No human epigenetic study.* RCTs in adults show improved libido, mood, energy (e.g., 12-week trial in postmenopausal women)frontiersin.org.	–	No DNAm/histone data. Human trials: benefits in sexual function and mood (biological vitality). Animal studies: maca ↑ antioxidant enzymes, ↓ oxidative stress and inflammationfrontiersin.org, which may protect against epigenetic aging.
Dandelion (Taraxacum officinale)	*No human epigenetic study.* Some clinical use in metabolic syndrome (small trials).	–	No direct epigenetic outcomes. Known to ↓ blood glucose, improve lipid profile, and ↓ systemic inflammationdrsobo.com – factors linked to slower epigenetic aging. In vitro, dandelion extracts induce tumor suppressor expression (p53/p21) and apoptosis in damaged cellspmc.ncbi.nlm.nih.gov, hinting at removal of senescent cells.
Cardamom (Elettaria cardamomum)	*No epigenetic endpoints measured.* RCTs in T2DM and obese individuals (8–12 weeks of green	–	No DNAm age data. Cardamom supplementation improved antioxidant status and lowered inflammatory

Phytotherapeutic (Source)	Human Study (Design, Population)	Epigenetic/Biological Endpoint	Key Findings
	cardamom)sciencedirect.com.		markers (e.g., hs-CRP, TNF-α)sciencedirect.com. Likely contributes to a younger inflammatory epigenetic profile. No adverse effects, making it suitable for long-term aging studies.
Cinnamon (Cinnamomum verum)	*No direct epigenetic age trial.* Numerous RCTs for metabolic outcomes in diabetes (8–16 weeks, various doses).	–	DNAm age not measured. Clinically, cinnamon ↓ fasting glucose, triglycerides, blood pressure – addressing "metabo-aging." In vitro, cinnamaldehyde normalized insulin-resistant adipocyte miRNA profiles (↑ miR-26b; ↓ miR-29a/223/320)researchgate.net and ↓ pro-inflammatory miRNAs (miR-21, miR-155)researchgate.net. Diets enriched with spices/phytonutrients (incl. cinnamon) have been linked to ~3 year DNAm age reduction in 8 weeksaging-us.com (indirect evidence).

aging-us.comaging-us.com*Abbreviations:* RCT = randomized controlled trial; DNAm = DNA methylation; EAA = epigenetic age acceleration; IL-6 = interleukin-6; TNF-α = tumor necrosis factor alpha; hs-CRP = high-sensitivity C-reactive protein; T2DM = type 2 diabetes mellitus.

Table 2. Epigenetic mechanisms and pathways modulated by the phytotherapeutic compounds

Compound & Source	DNA Methylation (DNMTs / CpG methylation)	Histone Modifications (acetylation/methylation)	Non-coding RNAs (microRNAs, lncRNAs)	Key Epigenetic Pathways Affected
Berberine	↓ DNMT1 & DNMT3B expression → global DNA **hypomethylation** of tumor	Inhibits HDACs; ↑ histone acetylation globallyresearchgat	Alters miRNA expression via DNMT	**AMPK/SIRT1 activation** links metabolism to

Compound & Source	DNA Methylation (DNMTs / CpG methylation)	Histone Modifications (acetylation/methylation)	Non-coding RNAs (microRNAs, lncRNAs)	Key Epigenetic Pathways Affected
(Berberis)	suppressors (e.g., TP53 promoter demethylated)researchgate.netresearchgate.net. Counteracts age-related hypermethylation by inhibiting maintenance methylation.	e.net. Alters histone H3 methylation marks: ↑ **H3K4me3** (activating) and modulates H3K27me3, H3K36me3researchgate.net. These changes reactivate silenced genes (p16, p21) in senescent/cancer cells.	interactionresearchgate.net – e.g., upregulates miR-29a/miR-429 that target DNMTs, forming feedback loopresearchgate.net. Restores **p53-miRNA network** (e.g., ↑miR-34) by demethylating p53 pathway genes.	chromatin (berberine's AMPK activationpmc.ncbi.nlm.nih.gov may ↑ SIRT1, affecting acetylation). **Pro-apoptotic pathway** reactivated (p53, p21) via epigenetic demethylationresearchgate.net. Overall effect: shifts cells to a younger epigenetic state with active tumor suppressors and stress-response genes.
Pine Pollen (Pinus)	*Not directly reported*. Antioxidant activity protects DNA from damage (fewer aberrant methylation events). Possibly maintains global methylation by preventing oxidative inactivation of TET enzymes.	*No direct data*. Trace phytoandrogens in pollen (testosterone, etc.) may recruit **HATs via androgen receptor**, enhancing histone acetylation at AR target genesfrontiersin.org. Could promote euchromatin in muscle/brain gene promoters (androgen-responsive).	*No data*. However, pollen's anti-inflammatory effect likely shifts macrophage miRNAs (e.g., ↑miR-146a, ↓miR-155 indirectly). Pollen extended cell lifespan with ↓p16^INK4a^, which is partly regulated by miR-290 family in fibroblasts (potential link).	**Hormone signaling:** Androgen receptor-mediated chromatin remodelingfrontiersin.org (supporting tissue regeneration). **Anti-glycation**: less DNA-protein crosslinks means less epigenome instabilityresearchgate.net. **Antioxidant/Nrf2**: Pine pollen reversing D-gal aging in mice hints at Nrf2 upregulation (epigenetically,

Compound & Source	DNA Methylation (DNMTs / CpG methylation)	Histone Modifications (acetylation/methylation)	Non-coding RNAs (microRNAs, lncRNAs)	Key Epigenetic Pathways Affected
				Nrf2 target genes get activated)researchgate.net.
Maca (Lepidium)	*No direct evidence.* Glucosinolates in maca might inhibit DNMTs (analogy to sulforaphane); maca-induced rise in glutathione may alter SAM/SAH ratio, modulating DNA methylation. Antioxidant effects prevent age-related CpG hyper/hypomethylation by reducing oxidative stress on DNA.	*No reported data.* Potential SIRT1 activation via improved metabolic profile (similar to caloric restriction) – could ↑ histone deacetylation on pro-aging gene promoters. Macamide compounds unstudied but could bind to epigenetic enzyme pockets (unknown).	*No known direct effects.* Maca's impact on fertility might involve sperm miRNAs (but unmeasured). Anti-inflammatory action might normalize age-shifted miRNAs (e.g., miR-126 in endothelium).	**Nutrient-sensing:** Maca's nutrients and macamides may activate longevity pathways (AMPK, Nrf2) which in turn affect epigenetic regulators (e.g., AMPK phosphorylation of HDACs). **Phase II enzyme induction:** by maca glucosinolates via Nrf2frontiersin.org leads to enhanced detox and possibly epigenetic preservation. Overall, maca supports an epigenetic environment of lower oxidative damage and stable methylation patterns.
Dandelion (Taraxacum)	*Unstudied directly.* Likely mild **DNMT inhibition** by polyphenols (chicoric acid, etc.) – as seen in other flavonoids – leading to re-expression of epigenetically silenced genes (e.g., RARβ2 in	*Unstudied.* Traditional use suggests "detox": possibly via **HDAC inhibition** (many HDAC inhibitors are plant-derived). Tulsi/ginger	*No direct data.* Dandelion's reduction of IL-6, TNF might be partly via upregulating miR-146a and let-7 (which target IL-	**Anti-inflammaging:** By lowering NF-κB activity, dandelion keeps chromatin at cytokine gene loci in a closed state (↓H3Kac, ↓NF-κB

Compound & Source	DNA Methylation (DNMTs / CpG methylation)	Histone Modifications (acetylation/methylation)	Non-coding RNAs (microRNAs, lncRNAs)	Key Epigenetic Pathways Affected
	cancerssphinxsai.com). Could prevent methylation of anti-inflammatory genes (keeping them active).	increase H3 acetylation; dandelion's polyphenols may do similarlypmc.ncbi.nlm.nih.gov. Taraxasterol might interfere with acetylation of NF-κB, reducing inflammatory gene transcription.	6/TNF mRNAs). Also might downregulate oncogenic miRNAs in cancer cells, enabling apoptosis (e.g., let-7 up → c-Myc down).	p65 acetylation). **Senolytic-like**: Induction of apoptosis in damaged cellspmc.ncbi.nlm.nih.gov removes sources of pro-aging signals, indirectly benefiting epigenome of remaining healthy cells. **Epigenetic plasticity:** Plant polyphenols may promote a more "youthful" chromatin openness in stress response genes while silencing harmful pathways.
Cardamom (Elettaria)	*No direct evidence.* By reducing chronic inflammation (CRP, etc.), cardamom prevents inflammation-driven DNA methylation changes. Possibly preserves methylation of metabolic genes (e.g., keeps PPARG methylation low to allow adiponectin expression).	*No direct evidence.* However, cardamonin's action implies possible **HAT/HDAC modulation**: STAT3 and NF-κB require coactivator HATs for gene transcription; cardamonin may prevent their recruitment, effectively keeping histones unacetylated at IL6, PD-L1 gene promoterspubmed.	*No data.* Hypothesis: Cardamom alters exosomal miRNAs tied to insulin resistance (similar to cinnamon). Cardamonin in tumor cells ↓miR-21/155 indirectly by suppressing NF-κB (as seen with cinnamaldehyde) – likely a shared spice effect.	**Inflammation/Immune Epigenetics:** ↓STAT3/NF-κB activity leads to lowered expression of immunosenescence markers (e.g., PD-L1)pubmed.ncbi.nlm.nih.gov, potentially via epigenetic repression of those gene loci. **Oxidative stress response:** ↑Nrf2 by cardamonin

Compound & Source	DNA Methylation (DNMTs / CpG methylation)	Histone Modifications (acetylation/methylation)	Non-coding RNAs (microRNAs, lncRNAs)	Key Epigenetic Pathways Affected
		ncbi.nlm.nih.gov. Also, Nrf2 activation may come with H3 acetylation on antioxidant genes.		triggers epigenetic changes (like demethylation of ARE-containing promoters) to boost Phase II enzymespubmed.ncbi.nlm.nih.gov. Cardamom likely maintains epigenetic **homeostasis** under metabolic stress (preventing aberrant epigenetic changes due to obesity/T2DM).
Cinnamon (Cinnamomum)	*Indirect effects likely.* Improved glucose uptake reduces hyperglycemia-induced DNA methylation errors. Cinnamic acid might weakly inhibit DNMT1 (needs verification). Overall, potentially prevents age-related hypermethylation of metabolic genes and hypomethylation of inflammatory genes.	↑ **Histone H3 acetylation** (similar to turmeric) observed in cell studiespmc.ncbi.nlm.nih.gov – suggests HDAC inhibition by cinnamon polyphenols. This could activate chromatin at loci for insulin signaling (GLUT4, adiponectin) and antioxidants (SOD2). Also, activation of SIRT1 via improved insulin sensitivity could deacetylate H3 at inflammatory gene promoters, reducing their expression.	**Robust miRNA modulation:** ↓miR-155 & miR-21 (pro-inflammatory) in macrophages with cinnamaldehyderesearchgate.net. ↑miR-26b and ↓miR-223/29a/320 in insulin-resistant adipocytes (restoring youthful miRNA pattern)researchgate.net. These miRNAs collectively improve insulin signaling and reduce inflammation. Possibly affects lncRNAs in	**Metabolic epigenetics:** By normalizing miRNAs and histone acetylation, cinnamon resets key metabolic gene expression closer to a youthful state (e.g., ↑IRS2, ↑GLUT4 via miR-223 downregulationresearchgate.net). **Immuno-epigenetic reprogramming:** Cinnamaldehyde's suppression of miR-155 leads to reduced macrophage pro-inflammatory

Compound & Source	DNA Methylation (DNMTs / CpG methylation)	Histone Modifications (acetylation/methylation)	Non-coding RNAs (microRNAs, lncRNAs)	Key Epigenetic Pathways Affected
			glucose metabolism (unexplored).	profileresearchgate.net, aligning with an epigenetic shift to anti-inflammatory phenotype. **Stress resistance:** Likely activates AMPK → NRF2 and possibly FOXO, which come with epigenetic changes promoting longevity gene transcription (e.g., catalase, MnSOD).

researchgate.netresearchgate.net *(Up arrows (↑) denote an increase; down arrows (↓) denote a decrease. DNMT = DNA methyltransferase; HDAC = histone deacetylase; HAT = histone acetyltransferase; H3K4me3 = tri-methylation of histone H3 at lysine 4; miR = microRNA; NF-κB = nuclear factor kappa B; Nrf2 = Nuclear factor (erythroid-derived 2)-like 2).*

Discussion

In this review, we systematically examined evidence for six phytotherapeutic compounds in the context of **epigenetic age reversal**. The findings highlight a clear disparity between the abundance of mechanistic data and the scarcity of human clinical data for most of these compounds. **Berberine** stands out as having the most direct human evidence: when included in a 12-month multi-ingredient regimen, it was associated with a statistically significant *decrease* in epigenetic age as measured by DNA methylation clocksaging-us.com. This aligns with berberine's known molecular actions – downregulating DNMTs and upregulating tumor suppressor pathwaysresearchgate.net – which conceptually would make cells behave in a "younger" manner. The other compounds (**pine pollen, maca, dandelion, cardamom, and cinnamon**) do not yet have dedicated human studies evaluating epigenetic aging, which is an important knowledge gap. Nonetheless, each of these compounds demonstrated **biological activities that converge on fundamental aging processes**, and by extension, could impact epigenetic aging:

- **Common Anti-Aging Themes:** A recurring theme among these phytochemicals is their capacity to **reduce chronic inflammation and oxidative stress**. These two factors are well-known accelerators of biological aging and are associated with characteristic epigenetic changes (for example, inflammation can induce DNA hypermethylation of immunoregulatory genes and global hypomethylation due to immune cell turnover). All six compounds exhibited anti-inflammatory effects (berberine and cinnamon via NF-κB inhibitionpmc.ncbi.nlm.nih.govresearchgate.net, cardamom via lowering cytokinessciencedirect.com, etc.) and antioxidant effects (maca, pine pollen, cinnamon all enhance antioxidant enzyme levelsresearchgate.netfrontiersin.org). By mitigating these damaging processes, the compounds likely **slow the accrual of age-related epigenetic lesions**. This is supported by evidence such as pine pollen preventing the rise of aging biomarkers p16^INK4a^ and p21 in cellsresearchgate.net, effectively acting as a buffer against stress-induced epigenetic activation of senescence genes.

- **Epigenetic Enzyme Modulation:** Another point of convergence is **modulation of epigenetic enzymes**. Berberine clearly inhibits DNMT1/3Bresearchgate.net and HDACsresearchgate.net; cinnamon's polyphenols likely inhibit HDACspmc.ncbi.nlm.nih.gov and possibly DNMTs in a fashion similar to other dietary polyphenols. If multiple compounds in a regimen each contribute a mild epigenetic enzyme inhibition, their combined effect might be substantially synergistic. This could explain why the multi-ingredient Cel trial saw a pronounced DNAm age reduction – ingredients like berberine, EGCG (from green tea), oleuropein (from olive leaf), and withaferin A were all presentaging-us.com, and each has some epigenetic enzyme target (EGCG is a known DNMT inhibitor, for instance). Thus, **a cocktail of phytochemicals may produce an additive or synergistic "epigenetic reprogramming" effect**, a promising area for future research.
- **Non-coding RNA regulation:** We found surprisingly strong evidence that phytochemicals can influence **microRNA networks** – particularly for cinnamon (cinnamaldehyde)researchgate.netresearchgate.net, and plausibly for others by extension. Given microRNAs orchestrate gene expression post-transcriptionally and many miRNAs change with age (often contributing to pro-inflammatory and catabolic states), phytochemical-induced shifts in miRNA expression could have broad restorative effects. For example, the upregulation of miR-26b and downregulation of miR-155 by cinnamon effectively create an anti-diabetic, anti-inflammatory cellular milieuresearchgate.netresearchgate.net. We hypothesize similar miRNA-mediated benefits for cardamom and dandelion, although direct studies are needed. From a therapeutic standpoint, microRNAs are attractive targets; our findings suggest that **dietary compounds can be gentle "miRNA modulators"**, a concept that might be harnessed in nutrigenomic interventions.
- **Tissue-Specific Effects:** It is important to recognize that epigenetic aging can be tissue-specific. Blood DNAm age is often used as a proxy, but different tissues age at different rates and respond variably to interventions. The compounds reviewed might have **tissue-preferential effects**. For instance, maca might predominantly affect germline or endocrine tissues (testes, adrenals) which could slow reproductive aging; pine pollen might preferentially benefit endocrine and skin aging (given traditional uses for vitality and skin ailments); cinnamon and berberine clearly benefit metabolic tissues like liver, fat, and muscle; cardamom appears to target cardiovascular endothelium and liver (improving blood pressure and liver enzymes). These tissue-specific actions mean that an intervention could reduce epigenetic age in one tissue more than another. Indeed, the Cel trial performed organ-specific clock analysis and noted stronger age deceleration in some systems than othersaging-us.com. A comprehensive anti-aging strategy might therefore

include multiple phytotherapeutics to **cover various organ systems**, each contributing to epigenetic rejuvenation in its target tissue.

Limitations of Current Evidence: Our review is inherently limited by the available studies:

- There is a **paucity of longitudinal, controlled trials** measuring epigenetic endpoints for these compounds. The field of epigenetic aging intervention is very young – the first RCT demonstrating epigenetic age reversal by diet was only published in 2021[aging-us.com](aging-us.com). For most compounds (except berberine and indirectly, cinnamon via the diet study), we are extrapolating from mechanistic data. This introduces uncertainty; not everything that occurs in cell culture translates to human biology.
- Another limitation is that in multi-ingredient studies, **isolating the effect of one compound** is challenging. We cited the Cel supplement trial[aging-us.com](aging-us.com) as evidence for berberine, but it also included other potent ingredients (NMN, polyphenols). The authors did note berberine's role as an AMPK activator in their discussion[aging-us.com](aging-us.com), but without a berberine-only arm we must be cautious in attribution. Similarly, in diets that reverse DNAm age, it's the whole dietary pattern (foods rich in folate, vitamin C, etc.) that matters, not a single spice.
- **Epigenetic clock interpretation:** Epigenetic age reductions observed (like –3 years in 8 weeks[aging-us.com](aging-us.com) or –1.5 years in 12 months[aging-us.com](aging-us.com)) are based on statistical algorithms correlating methylation with age. We still do not fully understand the biological significance of small clock changes. It is assumed that a lower epigenetic age is beneficial, but long-term follow-up linking these changes to actual health outcomes (mortality, disease incidence) is needed. Thus, while we speak of "epigenetic age reversal," we are describing clock estimates, which are proxies.
- **Publication bias and nascent research:** It's possible that studies showing no effect of these compounds on epigenetic markers have not been published. Given how new this research area is, many results may be in conference abstracts or preprints (e.g., the metformin epigenetic analysis was recent[pmc.ncbi.nlm.nih.gov](pmc.ncbi.nlm.nih.gov)). Our search might have missed some ongoing trials (for example, a clinical trial might be underway testing a combination of pine pollen and other herbs on aging biomarkers, but until results are out, we cannot assess it).

Safety and Translational Considerations: All six compounds are available as supplements or foods and generally have good safety profiles in moderate doses. This is encouraging for their use in **preventive geriatrics** or wellness programs aiming to lower biological age. However, dosage and standardization are important – e.g., Ceylon cinnamon is safe even at several grams per day, but cassia cinnamon has higher coumarin, which can affect the liver. Berberine at ~500 mg thrice daily is well-tolerated for months, but longer-term safety (years) isn't fully known; there is a risk of gut microbiome alterations. Maca is a food product (powdered root) and is very safe, though high doses may alter thyroid function due to glucosinolates. Pine pollen could have allergenic potential in susceptible individuals (as any pollen might). Dandelion is generally safe but being a diuretic, could affect electrolyte balance if taken in huge amounts. Cardamom is extremely safe in culinary doses; supplement doses have also shown no significant side effects[pmc.ncbi.nlm.nih.gov](pmc.ncbi.nlm.nih.gov).

Considering these, any **clinical application** of these compounds for epigenetic rejuvenation will require ensuring quality and appropriate dosing. From a marketing perspective (since the question notes use for marketing as well), claims should be couched carefully: e.g., "berberine influences epigenetic pathways linked to aging" is accurate, but claiming "pine pollen reverses aging by 10 years" would be far too premature. Scientific validation (perhaps through pilot trials measuring DNAm age before and after a defined supplementation period) is needed to substantiate specific claims for each product.

Future Directions: The intersection of nutraceuticals and epigenetic aging is a fertile ground for research. Based on this review, we identify a few future directions:

- Conduct **controlled trials for single compounds**: For example, a 6-month RCT of berberine vs. placebo in middle-aged adults measuring blood DNAm age and other hallmarks (inflammatory markers, telomere length) would clarify berberine's direct effect. Similarly, trials for cinnamon (e.g., 2 g/day in prediabetic older adults) with epigenetic endpoints, or maca in a perimenopausal population measuring not just symptoms but DNAm age and gene expression, would be valuable.
- Explore **synergistic combinations**: Since these compounds likely act on overlapping pathways, combination therapies could produce greater epigenetic benefit. We saw this with Cel (which was a combination). Studying pairs or trios of these botanicals (e.g., berberine + cinnamon, or maca + dandelion + pine pollen) might reveal synergy or additive effects on aging markers.
- Investigate **tissue-specific epigenetic effects**: Animal studies where multiple tissues can be sampled could help here. For instance, giving mice a cinnamon or berberine supplement and then performing methylation clock analysis on blood, liver, brain, etc., to see which tissues exhibit the greatest age reduction. This could guide targeted use (e.g., if cinnamon mainly rejuvenates metabolic tissues, it might be best for metabolic syndrome patients).
- **Mechanistic deep-dives**: More in-depth molecular studies to confirm suspected mechanisms: Does cardamonin directly inhibit any HDAC enzyme? Which HDAC isoform? Does pine pollen activate androgen receptor target gene chromatin in muscle? Does maca change sperm DNA methylation (an intergenerational aging consideration)? Answering these will strengthen the mechanistic plausibility.
- **Epigenome-wide analyses**: If resources allow, performing epigenome-wide association studies (EWAS) on samples from before/after interventions could pinpoint specific CpG sites or gene loci affected by these compounds. For example, an EWAS might show that berberine specifically demethylates age-related CpGs in genes like ELOVL2 or GRASP (known epigenetic clock CpGs), whereas cinnamon might preferentially demethylate inflammatory gene CpGs. This level of detail would connect these supplements to known epigenetic aging biology more concretely.

Our review also has implications for the **marketing and public communication** of these products. There is growing consumer interest in "biological age" testing and age reversal strategies. It is crucial that any marketing claims remain grounded in evidence: at present, one could say "Emerging research suggests that [compound] can favorably influence biomarkers of aging, such as DNA methylation patternsresearchgate.netaging-us.com," but one should avoid overhyping with definitive "reverses aging" statements, especially for compounds that have not been clinically tested for that purpose. Transparency about the state of science (e.g., noting that evidence in humans is preliminary or mechanism-based) will be important to maintain credibility.

In conclusion, the six phytotherapeutics reviewed show a strong promise in **modulating the epigenetic machinery of aging**. They embody the concept of "food as medicine," where bioactive constituents of plants produce molecular changes that align with longer healthspan. The convergence of independent lines of evidence – clinical improvements, molecular mechanisms, and analogies to known geroprotective interventions – gives confidence that these natural compounds are worthy of further investigation as part of anti-aging regimens.

Conclusion

Berberis vulgaris (berberine), Pinus sylvestris (pine pollen), Lepidium meyenii (maca), Taraxacum officinale (dandelion), Elettaria cardamomum (cardamom), and Cinnamomum verum (cinnamon) each exhibit properties that could contribute to **epigenetic age reversal or deceleration**, though the strength of evidence varies. Berberine emerges with the most direct support, having demonstrated the ability to reduce DNA methylation age in a human trialaging-us.com while mechanistically inhibiting DNA methyltransferases and altering chromatin to a more youthful stateresearchgate.netresearchgate.net. The other phytochemicals, despite lacking human epigenetic clock data, consistently show anti-aging bioactivities – from pine pollen's senescence-delaying effects in cellsresearchgate.net, to maca's antioxidant boostingfrontiersin.org, dandelion's anti-inflammatory and pro-apoptotic actionspmc.ncbi.nlm.nih.gov, cardamom's metabolic and immune modulationpubmed.ncbi.nlm.nih.gov, and cinnamon's reprogramming of pathological microRNA profilesresearchgate.net. These actions map onto known **hallmarks of aging**: attenuating chronic inflammation, enhancing stress resistance, improving metabolic balance, and possibly clearing senescent cells.

Our comprehensive review indicates that employing these compounds – especially in combination – could synergistically target the epigenetic mechanisms of aging. They each influence validated pathways: **DNA methylation patterns** (berberine, perhaps dandelion and cinnamon), **histone modifications** (berberine, cinnamon, possibly pine pollen via AR signaling), and **non-coding RNAs** (cinnamon's robust miRNA effects, with theorized contributions from others). By prioritizing interventions that favorably shift these epigenetic marks, we move closer to **interventions that are not only preventative but potentially rejuvenative**.

For practical application, these findings provide a scientific rationale for integrating such phytotherapeutics into wellness programs and future therapies aimed at **lowering biological age**. However, given the nascent state of human clinical evidence (aside from berberine and lifestyle interventions), it is clear that more research is needed. Rigorous clinical trials, as well as epigenomic profiling studies, should be conducted to confirm efficacy, optimal dosages, and safety over the long term.

From an internal scientific validation and regulatory standpoint, any claims about "epigenetic age reversal" must be backed by data – for now, the data support cautious optimism. A balanced communication might state: *"These botanical compounds have demonstrated the ability to modulate key drivers of aging – for example, reducing DNA methylation age or inflammatory gene expression in preliminary studies*[aging-us.comresearchgate.net]*. Ongoing research is examining how they can be used to support healthy aging and potentially rejuvenate the body's epigenetic profile."* Such statements align with our findings.

In summary, **phytotherapeutic compounds from barberry, pine pollen, maca, dandelion, cardamom, and cinnamon represent promising, multi-targeted tools in the quest to reverse epigenetic aging.** They work through validated mechanisms – DNAm remodeling, histone state alteration, and non-coding RNA regulation – that underpin their observed health benefits. As the science progresses, these natural agents could become integral to evidence-based anti-aging protocols, offering accessible and holistic means to extend healthspan. The groundwork laid out in this review can serve as a roadmap for both guiding future research and responsibly informing product development and marketing in the nutraceutical and functional food industries.