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Short communication

The phytochemistry of leaf senescence - from bioactive natural products to mode of action

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Introduction

Hidden beneath autumn's colors is an interesting biochemical process: chlorophyll is degraded into phyllobilins (PBs), linear tetrapyrroles that accumulate during chlorophyll breakdown. First characterized in senescent barley leaves in 1991 (Kräutler et al, 1991]), PBs have since emerged as a structurally diverse and widespread class of natural products. More than 70 PB structures have been described across different plant families (Karg et al, 2022), yet their full diversity remains unresolved.

PBs arise via the PaO/phyllobilin pathway, named for pheophorbide a oxygenase (PaO), the thylakoid membrane enzyme that opens the chlorin macrocycle to yield red chlorophyll catabolite (RCC), the first linear phyllobilin (Hörtensteiner et al, 1998, Kräutler 2016). RCC is rapidly converted to a primary phyllolumibilin (pPluB) and then diversified into modified phyllolumibilins (mPluBs) through, among others, changes at ring A and ring D. These intermediates are transported to the vacuole, where acidic pH induces a rapid, non-enzymatic tautomerization to colorless phylloleucobilins (PleBs) (Oberhuber et al, 2003, Tommasini et al, 1998). Subsequent oxidative steps, which are not yet fully defined, can generate yellow phylloxanthobilins (PxBs) and pink phylloroseobilins (PrBs) (Moser et al, 2008, Ulrich et al, 2011).

The analytical identification of PBs exploits their distinct UV-Vis characteristics. High-performance liquid chromatography with diode-array detection (HPLC-DAD) has proven central to PB discovery and annotation in complex plant extracts (Karg et al, 2022). A recently compiled UV database (https://www.photochemcad.com) facilitates PB identification by providing curated reference spectra for automated and comparative workflows.

Long regarded as detoxification products, PBs are now recognized as bioactive metabolites. Multiple *in vitro* and cellular assays support their antioxidant capacity (Wang et al, 2021). In *Echinacea purpurea*, six PxBs differing in their peripheral modifications and hence polarities showed potent antioxidant activity *in vitro,* comparable to caffeic acid; select members also scavenged reactive oxygen species (ROS) in cells (Karg et al, 2019). PBs can also modulate inflammation: a PxB from *Urtica dioica* inhibited COX-1 and COX-2 *in vitro* and reduced COX-2 protein levels in murine macrophages [Karg et al, 2021]. These findings suggest PBs may contribute to the health effects of medicinal plants.

Moreover, PxB and PrB, the pigments derived from chlorophyll degradation, display anticancer effects. *Cj*-PxB-2 from *Cercidiphyllum japonicum* was found to exert antiproliferative activities at low micromolar concentrations (Karg et al, 2020). The same structure occurs in *Echinacea purpurea* (*Ep*-

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PxB-6) (Karg et al, 2019). Further work revealed anti-migratory effects for both a PxB and a PrB, and identified actin as the first human cellular target of PBs (Karg et al, 2021 b). PB act as actin destabilizers, leading to perturbed cytoskeletal dynamics—an effect relevant to cancer progression, where actin remodeling plays a role for migration, invasion, metastasis, angiogenesis, and mechanotransduction. Notably, the heme-derived bilins bilirubin and biliverdin also bind actin, underscoring the translation of structural relation between chlorophyll- and heme-derived bilins into mode of action.

Conclusion and Outlook

Chlorophyll degradation has traditionally been viewed as a detoxification program during senescence (Kräutler & Matile, 1999). However, the pathway's enzymatic complexity, metabolic investment, and substantial PB accumulation suggest broader biological significance. Emerging evidence—spanning antioxidant, anti-inflammatory, and cytoskeleton-modulating actions—supports functional roles for PBs beyond end-products of chlorophyll disposal. These activities position PBs as contributors to the pharmacology of herbal remedies and as leads in natural product research.

Taken together, PBs are ubiquitous, structurally rich, and bioactive natural products arising from a highly orchestrated chlorophyll catabolic pathway. Advances in structural elucidation, spectroscopy-guided analytics, and cellular mechanistic studies have reshaped our understanding of potential benefits in human health. Continued mapping of PB diversity, clarification of the oxidative steps to PxBs and PrBs, and deeper target deconvolution will be key to translating these compelling leads into practical applications in phytotherapy, nutrition, and biomedicine.

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