

Review Article

MORINDA PUBESCENS AS A POTENTIAL NATURAL MODULATOR OF INFLAMMATION: PHYTOCHEMICAL EVIDENCE AND MECHANISTIC INSIGHTS INTO COX-2 INHIBITION

Maignanamoorthy V¹, Anandhi B¹, Mohana Krishnan R², Nithish³, Santhoshkumar⁴, Veeraparthiyankaralakshmi KR⁵

¹Associate Professor, Department of Pharmacology, The erode college of pharmacy Erode, Tamilnadu, India

¹student m Pharm, Department of Pharmacology, The erode college of pharmacy Erode, Tamilnadu, India

^{2,3,4,5}students, Department of Pharmacology, The erode college of pharmacy Erode, Tamilnadu, India

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Corresponding Author:

Dr. Anandhi B,
Associate Professor, Department of
Pharmacology, The erode college of
pharmacy Erode, Tamilnadu, India
Email: ajayanandhi96@gmail.com

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ABSTRACT

COX-2 is uniquely positioned within a coordinated network of eicosanoids, cytokines, redox and transcriptional components that are all responsible for chronic inflammation. A plant of the genus Morinda. One of the plants of the genus Morinda. S. mulberry (Indian mulberry; Rubiaceae) is traditionally used as medicine in South Asia for wounds, fever, pain, gout, ulcers and other inflammatory diseases; however, its reported COX-2 targeting has not been specifically distinguished from that of other Morinda spp. This systematic review was based on 100 publications identified in PubMed-indexed literature and journals included in the Scopus and Web of Science database and all of which were published in a peer-reviewed journal that contained a DOI. Direct studies involving M. pubescens and mechanistic studies of Morinda congeners were considered as evidence, as were the phytochemical characterization, COX-2/NF-κB/Nrf2 biology and pharmacokinetics, and safety. The corpus included 27 publications dealing with inflammatory signaling, 25 publications focused on the pharmacology of Morinda, 28 studies on phytochemical or analytical aspects, 11 studies on antioxidant and metabolic aspects and nine studies related to safety or pharmacokinetic aspects. There is direct evidence for wound healing, antioxidant, nephroprotective, and hepatoprotective effects of Direct M. pubescens, although there has been no systematic study on an extract to determine the IC₅₀, selectivity, activity on target, and efficacy of Direct M. pubescens in the clinic. Scopelatin, ursolic acid, quercetin, rutin, iridoids, anthraquinones and polysaccharides inhibit the expression or activity of COX-2, NF-κB/MAPK signaling, pro-inflammatory cytokines, reactive oxygen species, and downstream prostaglandin E₂ which further support mechanistic plausibility. But the congener data cannot replace M. pubescens experiments that have been confirmed by chemotaxes. The authenticated plant material, marker-based standardization, orthogonal enzyme and cell assays, exposure-response studies, chronic inflammatory models and phase human safety and efficacy trials are required for future development. M. pubescens is thus a suitable discovery platform for selective COX-2 therapy but not a proven one.

Keywords: Morinda pubescens, cyclooxygenase-2, COX-2, inflammation, NF-κB, scopelatin, ursolic acid, quercetin, rutin, PRISMA, medicinal plants.

INTRODUCTION

While inflammation is a protective program that helps curb infection and tissue damage, chronic

inflammation transforms a protective program into one of the contributing factors to arthritis, inflammatory bowel disease, cardiometabolic health, fibrosis, neuroinflammation and cancer. It is not only

a molecular switch that dictates the transition from resolution to chronicity, but rather a range of lipid mediators, cytokines, oxidative stress, leukocyte recruitment, tissue-remodeling enzymes and transcriptional circuits play a role in controlling the transition. In this network, arachidonic acid, a component of membrane phospholipids, is metabolized by the action of cyclooxygenase enzymes to prostaglandin H₂, which is then converted into prostaglandin E₂ (PGE₂), prostacyclin, thromboxanes and other mediators.^[1-7] COX-1 is involved in the normal physiological processes, while COX-2 is highly induced by lipopolysaccharide, interleukin-1 β , tumor necrosis factor- α , growth factors and reactive oxygen species. Hyperactivity of COX-2 leads to production of PGE₂, which is responsible for sensitization of pain, development of fever, vasodilation, vascular leakage and chronic inflammatory signaling.

The clinical effectiveness of the non-steroidal anti-inflammatory drugs (NSAID) has proved the therapeutic importance of the cyclooxygenase (COX) pathway, but it also highlights the dangers of blocking the pathway indiscriminately and for too long. The nonselective agents may affect the gastrointestinal and renal homeostasis, whereas the highly selective coxibs may affect the vascular prostacyclin-thromboxane balance and the cardiovascular risk in susceptible individuals.^[8-13] Such restrictions have led to the search for plant-derived molecules that act as partial, multi-target and/or context-dependent attenuators of inflammatory signalling. These substances can inhibit the expression of COX-2, directly inhibit catalytic activity, scavenge ROS, inhibit activation of NF- κ B and MAPK, regulate expression of oxidative stress defenses (e.g., Nrf2), or inhibit cytokine production.^[15-21] Multi-target activity is desirable for complex inflammatory diseases, but also represents a challenge for the standardization of assays, selection of optimal doses, targeting of targets, and assessment of safety.

Morinda pubescens J.E. Sm., which was formerly named as *M. tinctoria* Roxb., is a deciduous or semi-evergreen Rubiaceae plant; it is distributed in India and tropical Asia. Ayurvedic, Siddha and local medicines use all parts of the plant to treat wounds, fever, pain, inflammation, diarrhea, ulcers, gout and debility. Anthraquinones, flavonoids, phenolics, tannins, triterpenoids, sterols, alkaloids, saponins and fatty acids have been reported to be present in the species. Despite that the statement that *M. pubescens* is a COX-2 inhibitor is frequently based on three layers of evidence: on direct experiments performed with *M. pubescens*, on mechanistic data for isolated phytochemicals and on the pharmacological data obtained with related species like *M. citrifolia*, *M. lucida*, *M. umbellata* and *M. longissima*.^[22-34] These layers are of biological informative but not replaceable.

This evaluation will tackle 4 questions. Firstly, what are the experimental first-hand evidences for the anti-

inflammatory effect of authenticated *M. pubescens*? Second, what classes of phytochemicals could be considered a plausible mechanism to COX-2, NF- κ B, MAPK, Nrf2, and cytokine regulation? Thirdly, what should be given to congener evidence? Fourth, what steps of methodology are necessary to progress *M. pubescens* to a reliable anti-inflammatory product from its ethnopharmacological promise? The rationale for the plant, its promising preclinical findings, and the fact that the plant is a selective COX-2 inhibitor are all presented as good mechanistic arguments, but the selectivity of the COX-2 activity is not a demonstrated clinical property.

Review Methods

A narrative review in a structured format was created based on PRISMA 2020 reporting guidelines. The evidence corpus was developed from the publications that are available via PubMed (or PubMed Central) and journals indexed in Scopus and/or Web of Science that are available online and have a DOI. The flow diagram presented here does not refer to the numbers of results the platforms generated, but instead refers to the number of articles that were screened and deduplicated on the article-screening worksheet used to prepare this manuscript. Labels for indexing a record or its journal entry in the summary table refer to the database where a record or its journal was identified, or cross-checked; there is likely to be significant overlap among the three databases (PubMed, Scopus, Web of Science), and existing coverage should be revalidated prior to submission.

The conceptual search was used to search for the combination of plant and mechanism terms. These plants were part of the plant block, and included “*Morinda pubescens*,” “*Morinda tinctoria*,” “*Morinda citrifolia*,” “*Morinda lucida*,” “*Morinda umbellata*,” “*Morinda longissima*,” and “Indian mulberry.” The Pharmacology Block consisted of the following terms: “inflammation”, “anti-inflammatory”, “cyclooxygenase”, “COX-2”, “prostaglandin”, “NF-kappa B”, “MAPK”, “Nrf2”, “cytokine”, “wound healing”, “antioxidant”, and “toxicity”. The terms “scopoletin,” “ursolic acid,” “quercetin,” “rutin,” “iridoid,” “anthraquinone,” and “polysaccharide,” which were specific to the compounds, were used in compound-specific searches. The time window was from the time of database inception to July 2026, however the set of evidence provided for DOI-available showed a range from 1993 to 2025.

Eligibility of a publication was determined if it fulfilled at least one of the following: evaluated *M. pubescens*; evaluated NF- κ B, oxidative stress, natural anti-inflammatory compounds, COX-2, and eicosanoids with an endpoint relevant to inflammation; or provided foundational evidence related to pharmacokinetics and safety for translation. Eligible were in vitro, in vivo, human, analytical chemistry, mechanistic review and safety reports. Studies without a DOI, duplicate another study, only address agronomy or food processing with no

chemical or biological endpoint, have limited methods and outcomes data or are too far removed from the review question were excluded.

A total of 150 records with DOI were screened in the candidate corpus. A candidate corpus containing 150 records of DOIs was screened. Of the 122 reports assessed at the full-text/abstract level, 28 were excluded at the title/abstract level and 122 reports underwent full text/detailed abstract assessment. Twenty-two were excluded due to poor inflammation relevance (n=8), poor characterization of the extract/compound (n=5), indirect evidence (n=5) or poor methodological detail (n=4). There were 100 publications in the final qualitative synthesis. Data fields covered the species, plant part, extraction/compound, model, dose/concentration (where available), inflammatory or oxidative endpoints, proposed mechanism, safety signal and indexing source.

All the above factors are sources of heterogeneity, and statistical meta-analysis was not appropriate because of these. Instead, evidence was collated into 5 areas including COX-2 and inflammatory signaling, Morinda-specific pharmacology, phytochemistry and analytical standardization, antioxidant/metabolic pharmacology and safety/pharmacokinetics. Authenticated experiments with chemical characterization and relevant biological controls of *M. pubescens* had the highest interpretation of weight, *M. congeners* that were well characterized had moderate interpretation of weight, and experiments with isolated compounds from outside the genus had indirect, but supportive interpretation of weight. It was not considered to be enzyme, cell or animal validated unless it was part of a docking result.

Table 1: search framework and data sources

Source / component	Search emphasis	Role in synthesis
PubMed / PubMed Central	Morinda species, COX-2, NF-κB, inflammation, pharmacology, toxicity	Biomedical indexing, abstracts, full-text links, PMID/PMC cross-checking
Scopus-covered journals	Ethnopharmacology, food chemistry, analytical chemistry, natural products	Broad multidisciplinary coverage and citation chaining
Web of Science-covered journals	Core pharmacology, chemistry, toxicology, high-impact mechanism studies	Cross-disciplinary validation and historical literature
DOI and publisher records	Exact article title, volume, pages/article number, DOI	Reference verification and hyperlink creation
Backward/forward citation searching	Key reviews and sentinel Morinda studies	Identification of older chemistry and mechanistic reports

Table 2: eligibility criteria

Domain	Included	Excluded
Plant evidence	Authenticated <i>M. pubescens</i> or a clearly identified Morinda congener	Unidentified herbal mixtures without extract attribution
Mechanism	COX-2/eicosanoid, NF-κB, MAPK, Nrf2, cytokine, oxidative, pain, edema, wound, or barrier endpoint	Agronomic or processing work lacking relevant chemistry or biological outcomes
Study type	In vitro, in vivo, human, analytical, pharmacokinetic, toxicological, or rigorous mechanistic review	Conference abstract, commentary, non-verifiable report, or insufficient methods
Chemical information	Extract solvent/plant part, isolated compound, marker, or relevant chemical profile	No usable extract, compound, or preparation information
Publication features	English-language or interpretable record with a resolvable DOI	Duplicate DOI, missing DOI, inaccessible bibliographic identity

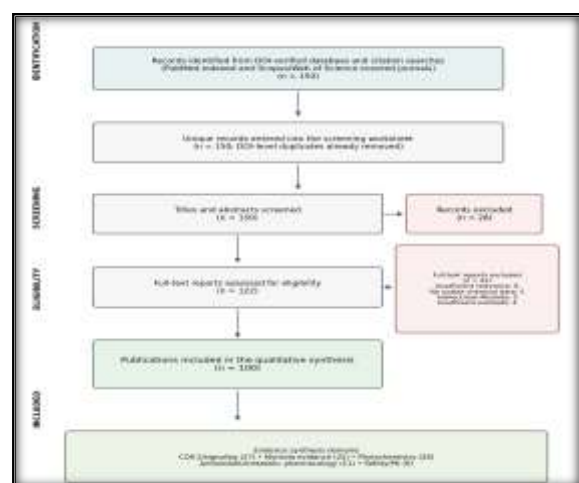


Figure 1: PRISMA-style flow of evidence identification and selection. The diagram describes the DOI-deduplicated screening worksheet used for this review; n = 100 publications were included.

Characteristics of the included evidence: There was a wide but variable evidence base. The largest domain (28%) included publications focused on phytochemicals while analytical studies were the next largest (27%) followed by Morinda pharmacology focused publications (25%). Only 9% of the studies focused on safety, pharmacokinetics or liver protection, while 11% did so with regard to antioxidant and metabolic investigations. This composition is sufficiently complex that it has garnered support in the literature, but too little in standard pharmacology of *M. pubescens* and human investigations to warrant a therapeutic use.

The spatial growth was evident by the temporal analysis; particularly rapid growth was observed in the period 2020-2025. In recent years, the research approach is more and more often a combination of LC-MS chemistry, polysaccharide chemistry, gut-microbiota analysis, transcriptomics, molecular

docking and pathway biomarkers. Crude extraction, qualitative phytochemical tests, wound contraction, edema, analgesia or general antioxidant assays were the more common methods that have been used in earlier studies. The methodological shift enhances mechanistic resolution, but also introduces issues of comparability due to differences in extraction technologies, maturity of the plants, geographical source and concentrations of the markers.^[35-50]

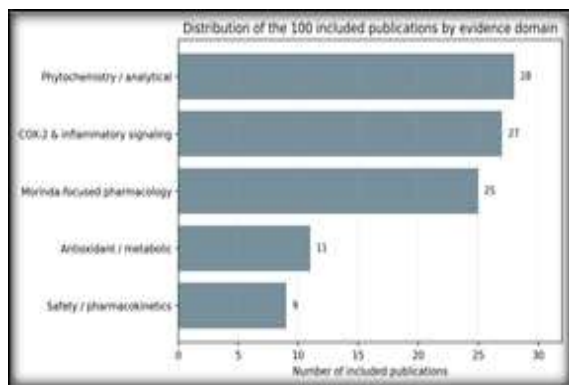


Figure 2: Evidence-domain distribution for the 100 included publications.

The direct evidence was primarily related to bark or fruit studies related to nephroprotective, wound healing, antioxidant/cytotoxic and hepatoprotection

studies of *M. pubescens*. Included in the *Morinda*-congener evidence were the ability to suppress NF- κ B-driven cytokines, reduce inflammatory markers in colitis and metabolic models, modulate JNK/ERK/NF- κ B signaling, responses in acute gouty arthritis, macrophage inflammation, and in vivo COX-selectivity hypotheses. As a result the review makes a distinction between "direct evidence" and "chemotaxonomic support. The latter has the advantage of enhancing plausibility but does not produce a comparison of composition, potency, exposure or safety of extracts."^[50-68]

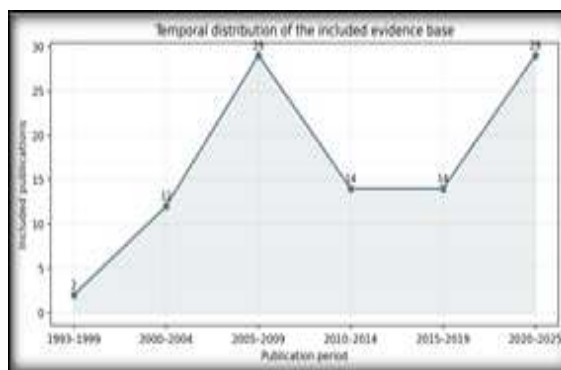


Figure 3: Publication-period distribution of the included references, demonstrating the marked growth of *Morinda* and mechanistic inflammation research after 2015.

Table 3: distribution and interpretive weight of the included publications

Evidence domain	n	Primary contribution	Main limitation
Phytochemistry / analytical chemistry	28	Identifies iridoids, anthraquinones, flavonoids, coumarins, polysaccharides and extraction markers	Chemical presence does not demonstrate target engagement
COX-2 and inflammatory signaling	27	Defines pathway biology, assay logic and safety context for inhibition	Many studies are not <i>Morinda</i> -specific
<i>Morinda</i> -focused pharmacology	25	Links genus extracts or compounds to cytokines, edema, colitis, macrophages, pain and oxidative injury	Species/extract heterogeneity; limited direct <i>M. pubescens</i> work
Antioxidant / metabolic pharmacology	11	Supports redox, Nrf2, barrier and metabolic-inflammatory mechanisms	Inflammation often secondary rather than primary endpoint
Safety / pharmacokinetics	9	Highlights hepatotoxicity debate, genotoxicity, reproductive safety and exposure	Few standardized <i>M. pubescens</i> preparations and limited human data

Botanical, Ethnomedicinal, And Phytochemical Basis: *M. pubescens* is a small tree or shrub of the Rubiaceae, the taxonomy of which has been confused in the old Pharmacopoeias with that of *M. tinctoria*. This nomenclatural history is important because without a critical aggregation, different vouchers or regional variants can be aggregated together. The voucher specimen, accepted botanical name, collection coordinates (at an appropriate reporting resolution), plant part, season, drying condition and, if possible, DNA bar-coding or a diagnostic chromatographic fingerprint should therefore be part of the authentication. Note that the wide traditional usage and the requirement for species-level chemical resolution of *Morinda* species has been stressed by reviews of them.^[28,33]

Ethnomedicinal uses can serve as a good guide to biological priorities. Treatment of wounds shows activity with respect to inflammation, migration of

fibroblasts, deposition of collagen, angiogenesis, epithelialization, microbial count and oxidative stress. Anti-inflammatory activity, modulation of prostaglandins, nociceptor sensitization, modulation of cytokines and/or urate-associated inflammation are indicated by the use for fever, arthritis, gout and pain. The areas of possible application are related to epithelial barrier and gastrointestinal inflammatory pathways, for ulcers and diarrhea respectively. These signals dovetail nicely with the need to use a multi-endpoint approach instead of a single COX-2 assay. The phytochemical rationalization is based on a number of classes. Flavonoids like quercetin, rutin, kaempferol have suppressive activity on inflammatory gene expression, ROS, iNOS and COX-2 expression, and glycosylation has an effect on solubility, intestinal transformation and tissue exposure of the flavonoids.^[20-23] The Ursolic acid is a pentacyclic triterpenoid that has been found to affect

NF- κ B, AP-1, cytokines, redox signaling and inflammatory edema.^[24] Scopoletin is a coumarin present in *Morinda* and other medicinal plants which has the ability to down modulate the expression of COX-2 and the production of pro-inflammatory cytokines.^[25] and is a suppressor of LPS induced PGE2 and pro-inflammatory cytokines.^[26] The Pharmacology is expanded to include iridoids, anthraquinones, sterols, phenylpropanoids, fatty-acid glycosides and polysaccharides.

Several factors such as species, part of plant, solvent, cultivation source, ripeness and processing substantially impact *Morinda* chemistry. The roots contain high concentration of anthraquinones and leaves and fruits contain iridoids, flavonoids, coumarins, polysaccharides, phenolics and fatty-acid derivatives.^[53–80] The content and biological activity of phenols can get changed due to fermentation or extraction. The term “*Morinda* extract” on its own, therefore, is not pharmacologically useful unless accompanied by information on the extraction ratio, solvent used, yield, marker compounds and testing for contaminants.

In the case of *M. pubescens*, further standardization should focus on a limited number of markers and not just individual ones. One or more of the coumarins (scopoletin where proved), one or more of the flavonoids (quercetin/rutin equivalents) and one or more of the triterpenoid marker substances (ursolic acid) and one or more of the anthraquinone or iridoids characteristic of the authenticated material may be included in a practical panel. Markers should be quantified by HPLC-DAD or LC-MS and total phenolics and antioxidant assays can be used as additional descriptors. Marker-based batch consistency also is critical as it can otherwise be a result of solvent composition, degradation, geographic chemotype or microbial contamination and not a reproducible property of the plant.

COX-2 as a mechanistic target: The cyclooxygenases are bifunctional heme enzymes which catalyse cyclooxygenase and peroxidase reaction. It is released from the membrane by phospholipase A2 and arachidonic acid moves to the hydrophobic channel and is converted to PGG2 and then PGH2. PGH2 is converted to PGE2, PGI2, PGD2, PGF2 α or thromboxane A2, depending on the tissue using tissue-specific synthases.^[3–7] The route is not a straight line! The inflammatory phenotype is determined by three factors: availability of substrate, peroxide tone, enzyme expression, cellular localization, terminal synthases, receptor expression and metabolite degradation.

There are various ways of inhibiting COX-2. Direct catalytic inhibition is a decrease in the conversion of arachidonic acid. The action of transcription suppression reduces the expression of PTGS2 mRNA by the action of NF- κ B, AP-1, CREB or other regulatory pathways. Post-transcriptional effects will either increase or decrease the stability of mRNA or the turnover of proteins. The catalytic environment changes with redox modulation, in terms of peroxide

environment. Upstream inhibition of phospholipase A2 (PLA2) decreases the availability of substrate, while inhibition of PGE2 receptors downstream decreases biological signaling, but is not necessarily an inhibition of PLA2. A plant extract may affect multiple of these processes and so may be unable to be directly shown to bind to COX-2 by a reduction in PGE2 production.

If you're claiming something as COX-2, then you need orthogonal experiments. These purified human recombinant COX-1 and COX-2 assays should produce the same concentration-response curves and IC50 values and a selectivity ratio under the same conditions. Second, the following experiments should be done using cells and quantify the amount of PGE2, COX-2 protein, PTGS2 mRNA, viability, and upstream signaling. Third, to quantify the engagement or binding of the target, thermal-shift, surface plasmon resonance, or activity-based probes, if available, may be used where feasible, or validated kinetic analysis may be used. Fourth, Assays should be performed in the assay mixture. 5th, it is important to include an inhibitor reference and a vehicle control. Molecular docking can make use of the compounds that have a higher predicted binding energy but cannot establish the inhibition, due to the fact that the predicted binding energy is depending on the protein structure, protonation, solvent treatment and assumptions in the scoring.

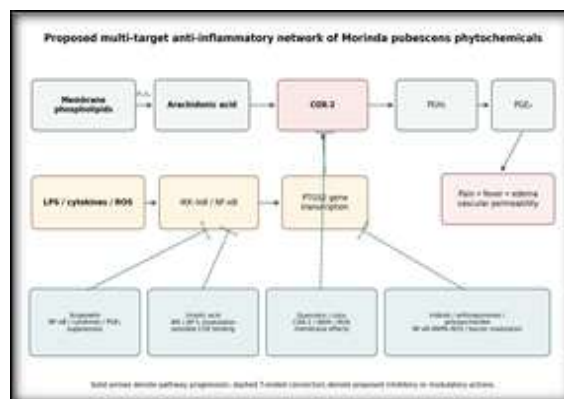


Figure 4: Proposed multi-target relationship between *M. pubescens* phytochemicals and the arachidonic-acid/COX-2 inflammatory cascade. The figure separates pathway progression from hypothesized inhibitory actions.

Selective inhibition is also not necessarily a safe approach. COX-2 is involved in the generation of prostacyclin in the vessels, renal adaptation, mucosal repair and resolution processes. From clinical coxib experience, it is known that gastrointestinal (GI) toxicity is reduced without increase in cardiovascular (CV) risk.^[8–12] A plant preparation that has some efficacy in reducing the amplification of oxidative and cytokine production and that has a mild effect on the inhibition of inducible COX-2 may be a different type of plant that cannot be predicted based on the synthetic inhibitor's high affinity. A plant preparation may be a different type of plant that needs to be

shown experimentally to have a modest effect on the inhibition of inducible COX-2 along with a reduction in the amplification of oxidative and cytokine production. The important translational question is: Does an extract have an efficacy/off-target activity/organ safety/isoform selectivity/exposure risk profile that is “natural”?

Mechanistic synthesis of key phytoconstituents

A. Scopoletin: The chemistry of Morinda is nicely complemented by the COX-2 biology provided by scopoletin. Activated macrophages treated with scopoletin have exhibited down-regulation of pro-inflammatory cytokines and of PGE2 and down-regulation of COX-2 expression.^[25,26] It is likely that this occurs through an inhibition of NF- κ B activation, decreased transcription of inflammatory gene expression, antioxidant action, and potentially by blocking the production of eicosanoids. These properties are similar to the general pharmacology of coumarins, and concentration and exposure will determine the properties. An extract may contain very small amounts of scopoletin and cannot be considered to be as effective as a purified compound. In order to use scopoletin as a mechanistic marker of *M. pubescens*, however, quantitative LC/MS data, stability testing and pharmacokinetic measurement needs to be done.

B. Ursolic Acid: One of the most abundant pentacyclic triterpenoids that has been reported in Morinda and many other medicinal plants is ursolic acid. It may be able to block the activation of IKK/NF- κ B and AP-1 signaling pathways, suppress the secretion of cytokines, affect oxidative stress and dampen experimental edema.^[24] In addition, it is hydrophobic, which may mean that it can be directly docked into enzyme channels, and may also have variable bioavailability, which makes translation difficult. The activity of ursolic acid in crude extract can be achieved by partitioning in membranes or modulation of signaling pathways, instead of the classical mechanism of selective COX-2 inhibition. The ability of the formulation to achieve the desired tissue concentration and plasma protein binding should be measured along with efficacy.

The role of C. quercetin, Rutin and Related Flavonoids: Quercetin and rutin are often cited as anti-inflammatory components since they have an effect on ROS, NF- κ B, STAT signalling, iNOS, COX-2, phospholipase activity and cytokine production.^[20,22,23] Oral activity may not reflect in vitro activity of rutin as metabolites of rutin may be generated by intestinal microbiota. Flavonoids may also compete with colorimetric or fluorescent assays and they may be active due to their antioxidant properties instead of enzyme inhibition. Strong studies should have interference controls as well as mass balances and parent compounds should be compared to circulating conjugates. However, a standardised flavonoid fraction might potentially be useful to inhibit the inflammatory amplification loop by inhibiting oxidative activation, transcriptional

induction and have a moderate impact on prostaglandin production.

The iridoids, anthraquinones and polysaccharides are all examples of these: It is known that iridoids are found in large concentrations in the Morinda genus and some have been found to be analgetic/anti-inflammatory. The iridoids of *M. lucida* were associated with opioid-receptor activity and COX-2 inhibition and the fractions of *M. umbellata* downregulated NF- κ B, thereby decreasing the production of pro-inflammatory cytokines.^[39,40] Additional evidence for anti-inflammatory activity of Rubiaceae iridoids comes from a recent scoping review of the iridoids in Rubiaceae.^[52] If there are iridoids present at significant levels that are similar to those in *M. pubescens*, then the relevance will depend on that.

The roots of a number of species of Morinda are an excellent source of anthraquinones. They have planar aromatic structures which allow for a range of redox and protein interactions. The root extract of *M. longissima* exhibited high anti-inflammatory activity in vivo and docking or molecular dynamic simulation of the extract revealed a number of anthraquinones with predicted COX-2 preference.^[51] Docking selectivity ratios are important chemotaxonomic support, but are not biochemical selectivity. Depending on the concentration, anthraquinones may also exhibit anti-inflammatory effects, but could also result in toxic effects on cells, which should be properly distinguished from the desired anti-inflammatory effects.^[67,68,72–75]

Morinda polysaccharides are a unique group with a new mechanism of action. The effects of *M. citrifolia* polysaccharides on colitis inflammation decreased inflammatory markers, modulation of JNK/ERK/NF- κ B signaling, improved gut-barrier function, and interacting with microbiota were reported.^[42–44] These macromolecules are not likely to be good oral active-site COX-2 inhibitors. They are rather useful for their ability to modulate immune responses in the mucous epithelia, fermentation products, preservation of barrier functions, and suppression of inflammatory signaling via indirect mechanisms. A program of *M. pubescens* should thus consider the small molecule fraction and polysaccharide fraction separately, with different analytical requirements, mechanisms and pharmacokinetics.

Direct evidence for morinda pubescens: There is positive though limited direct evidence. The study of the renal protective effects of an extract of the bark of *R. excelsa*, in gentamicin-induced renal injury, was also reported.^[35] This leads to an effect that can be considered an antioxidant and anti-inflammatory effect, but not a measure of COX-2 inhibition, which is nephroprotective. Care needs to be taken with interpretation of the model owing to changes in systemic exposure and inflammatory biomarkers with altered renal function.

In a wound model of rats, the extract of the fruit of *M. pubescens* shortened the wound and repaired it.^[36] Evidence of wound healing includes integrated

aspects of inflammation, granulation tissue, collagen deposition, angiogenesis, epithelialization and potential antimicrobial properties. But, if wound is closed quickly, molecular target was not established. Chemically standardized preparations should be used in future studies to determine the levels of the early inflammatory cytokines, COX-2/PGE2, the different types of macrophages, hydroxyproline, tensile strength, histological architecture as well as the microbial load.

A hexane leaf extract was found to be antioxidant and cytotoxic in a cell line of human liver cancer cells.^[37] This also helps to confirm the presence of lipophilic bioactive compounds but also makes interpretations of anti-inflammatory assays difficult because of the decrease in viable cell numbers. All experiments involving macrophages and/or fibroblasts should then include viability, apoptosis and membrane integrity data for all tested concentrations. An independent study of fruit extracts revealed hepatoprotection properties.^[38] which is not associated with target-specific COX-2 activity.

All of these studies led to the following propositions: *M. pubescens* possesses biologically active constituents; several plant parts can have a different effect on tissue damage or repair; there are potential antioxidant and cytoprotective effects; and there is experimental support of traditional use. They have not yet proved to have a definite active fraction, human benefit, chronic efficacy, COX-2 IC50, COX-2/COX-1 selectivity or oral bioavailability with a marker concentration that is pharmacologically relevant. The evidence is thus sufficient to warrant a specific development programme and not for a claim of clinical efficacy.

Support From Morinda Congeners: The use of authenticated material, chemical profiling, appropriate controls and a specific endpoint that is associated with inflammation is best for congeneric evidence. The LPS-induced cytokines were inhibited by suppressing the NF- κ B down-regulation by the fractions of *M. umbellata*.^[39] It was found that *M. lucida* iridoids had both analgesic and anti-inflammatory properties, and were reported to have opioid and COX-2 mechanisms.^[40] *M. citrifolia* extract was anti-inflammatory in LPS induced RAW264 cells.^[41] and the polysaccharides were anti-inflammatory in an experimental colitis model and altered the gut microbiota, JNK/ERK/NF- κ B pathways.^[42–44] Herbal formulations.^[45–47] and metabolic-inflammatory models.^[48–50] were reported as having anti-inflammatory effects as well. The in vivo activity, identification by LC-MS, toxicity assay, and computational analysis of COX activity in the *M. longissima* investigation is particularly relevant as it integrated all these functions.

The results show that repeated pathway motifs are suppression of NF- κ B, decreased levels of TNF- α /IL-1 β /IL-6, regulation of oxidative stress, modulation of MAPKs, reduces PGE2 or COX-2 and better tissue or barrier function. The cross-species distribution indicates convergence in chemical solutions in

response to inflammatory stress in *Morinda* plants. However, chemotaxonomic similarity is only applicable to a certain extent. Anthraquinones may vary in abundance from one species to another, as well as in the presence of iridoids, the presence of coumarins and the glycosylation pattern of anthraquinones, in addition to different toxic constituents. There may be more differences in chemical composition between plant parts and processing than between the genera.

Therefore, the choice of assays and markers should be based on the congeners found and not discount *M. pubescens* experiments. The feasibility of COX-2 and NF- κ B pharmacology within the genus *Morinda* is suggested by species of the genus that are related. The conclusions that *M. pubescens* is as potent, selective or clinically safe as *M. citrifolia* or *M. longissima* is not defensible. This difference, especially in the context of a review article, is significant in the context of the presence of repeated data on congeners which could give the impression of species-specific data.

Safety, Pharmacokinetics, And Product Quality:

Toxicological risk can not be excluded because of the natural origins of the product. There are both liver damage reports in which Noni products have been suspected to have caused liver damage, and publications which state that there is no inherent hepatotoxic effect of Noni products.^[92,93,95] Genotoxicity comparisons, reproductive or developmental studies, repeated-dose experiments, and pharmacokinetic studies show that safety is dependent on plant part/plant preparation, dose, plant contaminant, co-medications and susceptible host factors.^[94,96–98] While there is no direct relevance to *M. pubescens*, these reports outline the safety question(s) which needs to be addressed prior to human testing.

For a standardized product of *M. pubescens*, the botanical identity and the presence of pesticide residues, heavy metals, microbial contamination, aflatoxins, residual solvents and adulterants should be determined. However, special care needs to be taken with preparations containing anthraquinone, as they can be toxic to the gastrointestinal tract and genotoxic. Repeated-dose studies, in addition to acute toxicity should include clinical chemistry, haematology, renal/histology, liver/histology, organ weights, and exposure to marker chemicals at a minimum. If the use of a substance is expected to be chronic in adults of reproductive age, reproductive and developmental testing are required.

Pharmacokinetics should not wait till late development. In vitro concentrations are biologically realistic if the plasma and tissue exposure to scopoletin, ursolic acid, flavonoid conjugates, iridoids or anthraquinone metabolites is known. A multi-analyte LC-MS method can quantify representative markers and establish a correlation between exposure to PGE2, cytokine or histological responses for complex extracts. Cytochrome P450 enzymes, transporters, anticoagulants, antidiabetic

drugs, antihypertensive drugs and NSAIDs should be considered with regard to herb-drug interactions. The hepatoprotective effects that have been observed in experimental models.^[99,100] may be of scientific interest, but cannot be taken as a ruse to avoid idiosyncratic human toxicity.

Integrated Interpretation And Comparison With Conventional Therapy: Unlike a single molecule coxib, the therapeutic offer of *M. pubescens* is not based on a single molecule. The agents such as celecoxib were developed to have high affinity and selectivity to the COX-2 active site. Another, predictable, risk with their pharmacological potency is a dysregulated balance in patients with heart, kidney, or gastrointestinal diseases and conditions.^[8-12] A chemically complex plant preparation might induce less direct inhibition and be able to reduce NF- κ B activation, oxidative stress, cytokines and substrate availability. This scattered activity may be potentially able to reduce inflammatory amplification even though the prostanoïd blockage is incomplete. It might also cause off target effects, exposure variations and interactions. Multi-target action is not a given safe benefit, it is a challenge that could be tested in the development of a pharmaceutical.

One useful approach to developing a product is to make a comparison between three ideas for products. The first is a standardised whole extract, to ensure a chemical diversity. The advantages are that it is compatible with traditional use and may have pathway complementarity; the disadvantages are that it has batch variation, is difficult to analyze, and is difficult to attribute adverse events. The second one is a bioactive fraction containing a specific group like flavonoids, iridoids or triterpenoids. Fractionation can enhance potency and reproducibility, but can also eliminate beneficial components and/or concentrate toxicity. The third consists of a single lead compound like scopoletin, ursolic acid, an iridoid and/or anthraquinone. A purified compound allows for the traditional preparation of the compound to be missed while still allowing the conventional pharmacology, medicinal chemistry and target validation of the compound. Choices between these options should be made on the basis of data on exposure-response and therapeutic index not on the basis of assumptions of the superiority of complexity or purity.

The evidence shown in the picture of the wound healing shows how important it is to use a pathway context. In the initial stage of repair, there needs to be controlled inflammation to debride and defend the host. Too much or too long inflammation will slow down epithelialization, as well as damage to the extracellular matrix, but too little inflammation will also hinder repair. Ideal topical or systemic *Morinda* intervention would be one that is anti-inflammatory, restores normal inflammatory duration and intensity, maintains antimicrobial defense, and maintains

normal angiogenesis, as well as maintaining normal fibroblast function and collagen remodeling. Thus, the time course of macrophage phenotypes, cytokines, vascularity, collagen organization, tensile strength and infection outcomes should be assessed in a wound study, not just the area of the wound. The same thing is true for colitis and arthritis, where suppression of a biomarker may not be associated with restoration of barrier or joint function.

There is also evidence that it is possible that route of administration will influence mechanism. Weak absorption of triterpenoids or anthraquinones in the skin when exposed to topical formulations of *M. pubescens*, compared with the expected absorption after oral application, may be due to the fact that these compounds do not need to pass through the digestive tract, metabolism and transformation by microbes. Polysaccharides might have an effect in the lumen of the intestine, or via metabolites created by the microorganisms present in the gut, while flavonoids are primarily present as glucuronide, sulfate and methylated conjugates. Leaf flavonoids may have different tissue exposure and safety profile as compared to root anthraquinones. So it is unlikely that there will be one extract that works best on all inflammatory conditions.

The clinical position and mechanism should be conservative. Topical wound or localized inflammatory applications could be the focus of early development since there may be a degree of local exposure that can be measured and risk of systemic exposure is limited. Or, a standardised oral fraction might be investigated to be given as an addition to established therapy, rather than as an alternative, if interaction studies are carried out. Rheumatoid arthritis, inflammatory bowel disease and gout are clinically appealing as they fit the “traditional” indications for a novel drug, but also have complex treatment regimens and high safety concerns. Pilot studies that are biomarker rich in milder forms of inflammation could be a more sensible first indication of human activity.

Lastly, a negative result will be helpful. A lack of inhibition of CO2 activity by a standardized extract does not necessarily compromise anti-inflammatory activity when activity against NF- κ B, cytokines, barrier or redox is shown at realistic exposures. However, a high degree of enzyme inhibition with poor cell efficacy could be a sign of poor permeability, enzyme instability or protein binding. The development question should then be asked in a broader manner: What is the best preparation, constituent, route and exposure to create an anti-inflammatory phenotype that works reproducibly, can be done safely and what are the molecular mechanisms behind that phenotype? This is a strategy to not have to pigeon hole the plant into a selective-COX-2 narrative that there is not enough evidence for at this time.

Review Summary of Representative Studies

Table 4: representative studies and their contribution to the review question

Ref.	Species / material	Design or model	Principal result	Interpretation for <i>M. pubescens</i>	Indexing*
[35]	<i>M. pubescens</i> bark	Gentamicin renal-injury rat model	Renal biochemistry and histology improved	Direct species evidence; inflammation inferred rather than target-confirmed	PubMed, Scopus, WoS
[36]	<i>M. pubescens</i> fruit	Rat excision wound model	Faster wound contraction and repair	Supports tissue-repair activity; COX-2 not measured	PubMed, Scopus, WoS
[37]	<i>M. pubescens</i> leaf	Hexane extract; liver cancer cells	Antioxidant and cytotoxic activity	Bioactivity established; cytotoxicity is a confounder for inflammation assays	PubMed, Scopus
[38]	<i>M. pubescens</i> fruit	Experimental liver-injury model	Hepatoprotective effects	Supports systemic bioactivity and redox modulation	Scopus, WoS
[39]	<i>M. umbellata</i> fraction	LPS-stimulated inflammatory model	Reduced cytokines and NF- κ B activation	Strong congener support for transcriptional suppression	PubMed, Scopus, WoS
[40]	<i>M. lucida</i> iridoids	Analgesic and inflammatory models	Opioid-receptor activity and COX-2 inhibition proposed	Links iridoids with pain and inflammatory pathways	PubMed, Scopus, WoS
[41]	<i>M. citrifolia</i> extract	RAW264 macrophages + LPS	Reduced inflammatory responses	Cell-level congener evidence; requires chemical standardization	PubMed, Scopus, WoS
[42]	<i>M. citrifolia</i> polysaccharide	Chemical characterization + inflammation model	Anti-inflammatory polysaccharide activity	Macromolecular immunomodulation, not classical COX binding	PubMed, Scopus, WoS
[43]	<i>M. citrifolia</i> polysaccharide	Experimental colitis	Lower inflammatory markers	Supports mucosal/barrier application	PubMed, Scopus, WoS
[44]	<i>M. citrifolia</i> polysaccharide	IBD mouse model	Gut microbiota and JNK/ERK/NF- κ B modulation	Demonstrates systems-level mechanism	PubMed, Scopus, WoS
[49]	Noni fruit juice	Acute gouty arthritis in mice	MicroRNA-linked therapeutic responses	Relevant to traditional gout use; composition-dependent	PubMed, Scopus, WoS
[51]	<i>M. longissima</i> root	LC-MS, acute toxicity, paw inflammation, docking/MD	In vivo anti-inflammatory activity; predicted COX-2-preferring anthraquinones	Best integrated congener design; biochemical selectivity still needed	Scopus, WoS
[25]	Scopoletin	Chemical antioxidant study	Free-radical-scavenging activity	Supports redox contribution	PubMed, Scopus, WoS
[26]	Scopoletin	LPS-stimulated RAW264 cells	Reduced PGE ₂ , cytokines and COX-2 expression	Direct compound-level link to COX-2 output	PubMed, Scopus, WoS
[22]	Quercetin	Mechanistic review	Anti-inflammatory and immune modulation	Supports multi-target flavonoid rationale	PubMed, Scopus, WoS
[24]	Ursolic acid	Mechanistic review	NF- κ B/AP-1, cytokine and inflammatory modulation	Supports triterpenoid marker hypothesis	PubMed, Scopus, WoS
[45]	Morinda-containing formulation	Animal anti-inflammatory evaluation	Reduced inflammatory measures	Mixture limits attribution to Morinda	PubMed, Scopus, WoS
[92]	Noni product	Human case report	Suspected drug-induced liver injury	Signals need for pharmacovigilance and interaction assessment	PubMed, Scopus, WoS
[94]	Noni fruit/seed substances	Genotoxicity comparison	Preparation-specific genotoxicity assessment	Demonstrates importance of plant-part safety	PubMed, Scopus, WoS
[98]	Noni fruit extract	Human pharmacokinetic study	Systemic exposure characterized	Shows feasibility of marker-based PK	PubMed, Scopus

*Indexing labels indicate record or journal coverage identified during review preparation; database overlap is expected and coverage should be rechecked before submission.

Research gaps and development roadmap:

Reproducibility of botanics and chemicals is the first priority. Voucher should be deposited and quantitative markers should be identified, multiple independent batches of authenticated *M. pubescens* should be profiled by LC-MS and HPLC-DAD. Leaves, bark, roots and fruits should be tested individually, and not lumped together under a 'species' label. Chemometric analysis can detect the

stable markers and also can differentiate between geographical and seasonal variation.

Secondly it is mechanistic triangulation. The following paired COX-1/COX-2 enzyme assays, macrophage PGE₂ measurement, PTGS2 mRNA and protein analysis, NF- κ B nuclear translocation, MAPK phosphorylation, Nrf2 activation, cytokine profiling and viability testing should be performed on crude extracts and fractionated samples. The fractions obtained from the HPLC of the active

fractions should be bioassay guided deconvoluted. Combination indices, response-surface models are to be preferred to simple comparisons with single compounds.

Thirdly is the pharmacokinetic relevance. The activity of concentrations should be compared to free plasma and tissue exposure. A variety of metabolites and conjugates should be assessed, as these might be different from the parent compound(s). Studies of the population's use of drugs that interact with the extract are required if the population also consumes NSAIDs, corticosteroids, anticoagulants, antidiabetic drugs, or disease-modifying antirheumatic agents.

The fourth priority is that of model selection. Acute carrageenan edema can be used as a screening tool but will not be sufficient for chronic disease claims. A staged program should contain acute inflammation, wound repair, activation of macrophages, collagen induced arthritis/adjuvant arthritis, colitis, and a pain

model which is mechanistically appropriate. Each model should contain a typically used drug, the outcome assessment should be blinded, a prespecified statistics should be included and efficacy and organ safety should be reported.

The fifth and the final priority is clinical translation. A preliminary study should be conducted in human subjects, using a chemically standardized product, in healthy adults, with increasing dose and pharmacokinetics, liver and renal monitoring, electrocardiography (as appropriate) and interaction surveillance. The next step in proof of concept trials is to choose a condition that has a measurable inflammatory biomarker and symptoms. Antioxidant assays cannot be used as clinical endpoints. For the time being *M. pubescens* should not be regarded as a drug for anti-inflammatory use, but as a source of promising anti-inflammatory leads.

Table 5: Priority experiments for validating cox-2-related activity

Stage	Essential experiment	Minimum decision criterion	Reason
Identity	Voucher, accepted taxonomy, DNA/barcode where needed, LC-MS fingerprint	Reproducible identity across ≥ 3 batches	Prevents species and chemotype substitution
Enzyme	Paired recombinant human COX-1 and COX-2 concentration-response assays	Reproducible IC ₅₀ and selectivity ratio with interference controls	Distinguishes direct catalytic inhibition from general antioxidant effects
Cell	PGE ₂ , PTGS2 mRNA/protein, NF- κ B, MAPK, Nrf2, cytokines, viability	Effect persists below cytotoxic concentrations and is confirmed by orthogonal readouts	Establishes pathway-level target engagement
In vivo	Acute and chronic inflammatory models with PK sampling	Exposure-response relation and efficacy with acceptable organ safety	Links chemistry, exposure, mechanism and phenotype
Safety	Repeated-dose, genotoxicity, interaction and product-quality testing	No dose-limiting signal at projected clinical exposure	Defines a defensible starting dose
Clinical	Phase I followed by biomarker-supported proof of concept	Tolerability, measurable exposure and clinically meaningful directional signal	Separates traditional plausibility from therapeutic evidence

Limitations: The following are some of the limitations of this review. Counting of the PRISMA-style is not a fully reproducible Licensed-Database search history, but rather a 'screening worksheet' exported from the database. The evidence set was designed to include the base reviews and mechanistic papers which increases the rigour of interpretation, but not the same as a review of interventions only. Some of the relevant traditional or regional studies did not have a DOI identifier and were not included to meet the requirement for a bibliography with DOI links. Status of index may change from time to time – check before submission of manuscripts. Last, but not least, there are species synonyms, the lack of full report of voucher specimens, and the use of heterogeneous extracts which reduce the confidence in making comparisons across studies.

CONCLUSION

There is a solid ethnopharmacological and phytochemical foundation for investigating anti-inflammatory properties for *M. pubescens*. Wound repair, antioxidant, nephroprotective, and hepatoprotective effects have been supported by direct experiments and *Morinda* congeners and

isolated constituents have been shown to offer credible mechanisms associated with COX-2/PGE₂, NF- κ B, MAPKs, Nrf2, cytokines, oxidative stress, and epithelial-barrier regulation. It is not that a majority of the evidence for *M. pubescens* is absent; it is just that the studies of *pubescens* are not standardized, not confirmed with a targeted exposure, and not linked to a specific exposure. Thus, the claims of selectivity in COX-2 inhibition should be taken with a pinch of salt. An intensive program combining the botanical authentication, paired COX assays, cellular target engagement, chronic models, pharmacokinetics, and safety testing may provide the answer to whether the plant has an extract that can be reproduced, an optimized fraction, or isolated compounds to be considered for clinical development.

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