MEDICINAL PLANT-MEDIATED REGULATION OF RELAXIN HORMONE TO MITIGATE PRETERM BIRTH RISK: A REVIEW AND PROPOSAL FOR FUTURE RESEARCH

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Abstract: *Relaxin is a peptide hormone with roles in cervical remodeling, extracellular matrix modulation, and vasodilation during pregnancy. Elevated relaxin levels, or hyperrelaxinemia, have been associated with preterm premature rupture of membranes (PPROM) and increased risk of spontaneous preterm birth. Currently, conventional pharmacologic options to modulate relaxin are limited, and the potential of medicinal plants (phytomedicines) to regulate relaxin has not been systematically explored.*

Objective: *To review existing evidence on the role of relaxin in preterm birth, to examine any studies of medicinal plants or plant-derived compounds that might influence relaxin expression or action, and to propose experimental and clinical strategies to test and improve plant-based interventions for controlling relaxin and reducing preterm birth risk.*

Methods: Literature search was conducted in PubMed, Scopus, Google Scholar, and ethnobotanical databases up to mid-2025. Search terms included “relaxin”, “preterm birth”, “PPROM”, “medicinal plants”, “phytochemicals”, “natural compounds”, “hormone modulation”. Inclusion: human, animal, or in vitro studies about relaxin in pregnancy; studies of plants or plant compounds affecting relaxin, extracellular matrix, metalloproteinases (MMPs), cervical remodeling. Fifteen sources were selected. Gaps in the literature are identified; conceptual diagrams are proposed showing pathways of relaxin regulation and possible plant-compound intervention points.

Results: Relaxin is produced systemically by the corpus luteum and locally (decidua, placenta, fetal membranes). Elevated relaxin or slower decline in relaxin in mid-pregnancy is associated with preterm birth. Relaxin promotes MMP-1, MMP-3, reduces TIMP-1, affects cervical collagen, contributing to cervical softening and membrane rupture. However, no published controlled studies were found showing medicinal plants directly lowering relaxin levels or binding its receptor in human pregnancy. Some plants are known to modify hormone levels (estrogens, progesterone)

or reduce MMP activity (e.g., green tea catechins, flavonoids), but empirical evidence specific to relaxin is absent.

Conclusion: There is a plausible biological basis for using medicinal plants to control relaxin or its downstream effects (e.g., MMP activity, inflammation, ECM remodeling) to reduce preterm birth risk. Future research should include in vitro screening of phytochemicals for relaxin expression/receptor modulation; animal models; safety studies in pregnancy; then clinical trials.

Introduction: Preterm birth (delivery before 37 completed weeks of gestation) remains a global health problem, contributing significantly to neonatal morbidity and mortality. Among the mechanisms implicated in spontaneous preterm birth, the loosening of fetal membranes (premature rupture) and cervical remodeling are especially important. Relaxin (RLN), a peptide hormone secreted by the corpus luteum, decidua, placenta, and fetal membranes, has been found to play a role in these processes.

Elevated circulating relaxin (or slower decrease during mid-pregnancy) is associated with increased risk for preterm birth. For example, in a prospective study of ~2,846 women, those who later delivered preterm had higher levels of serum relaxin in second and third trimesters, and their relaxin levels declined less steeply than in term deliveries. Also, relaxin expression in decidua and fetal membranes is increased in cases of preterm premature rupture of membranes (PPROM).

Current preventive and therapeutic options for preterm birth (e.g., tocolytics) do not specifically target relaxin regulation. Medicinal plants or phytochemicals offer potential as modulators of biological pathways (e.g., reduction of matrix metalloproteinases, anti-inflammatory action, modulation of hormone levels). However, the evidence that plant-based treatments can regulate relaxin in pregnancy is lacking.

This article aims to:

1. Review what is known about relaxin's roles in preterm birth.
2. Examine any existing evidence of medicinal plants or phytochemicals that could affect relaxin expression or its downstream mechanisms.
3. Propose experimental and clinical pathways to evaluate plant-based interventions to modulate relaxin, with a view toward reducing preterm birth risk.

Results:

Role of Relaxin in Preterm Birth

From the literature:

- Relaxin is produced by both systemic sources (corpus luteum) and local tissue (decidua, placenta, fetal membranes).
- Elevated relaxin or less rapid decline in relaxin in the second and third trimesters is associated with spontaneous preterm delivery.
- Relaxin increases expression of matrix metalloproteinases (MMP-1, MMP-3) and decreases TIMP-1 in cervical tissues. In animal models, relaxin alters cervical collagen content and extracellular matrix remodeling.

- Relaxin binding receptor expression (e.g. LGR7) is upregulated in fetal membranes in PPROM cases.

Evidence of Medicinal Plants Affecting Relaxin or Related Pathways

- **No direct evidence** was found of medicinal plants demonstrated in human or animal pregnancy to lower relaxin hormone levels or block its receptor.
- Some plant compounds have documented action on **matrix metalloproteinases** or **inflammation / oxidative stress**, which are downstream of relaxin effects:

Plant / Compound	Effect on MMPs / ECM / Inflammation	Relevance to Pregnancy / Safety
Green tea catechins (epigallocatechin-gallate, EGCG)	Inhibit MMP-2, MMP-9 in various tissues; reduce inflammation in vitro.	Some caution: in high doses, effects in pregnancy unclear; limited human pregnancy studies.
Curcumin	Inhibits MMPs, suppresses NF-κB pathway, reduces inflammation.	Safety at certain doses shown, but systemic effects and bioavailability concern; limited pregnancy trials.
Resveratrol	Anti-oxidant, anti-inflammatory, shown to reduce MMP expression in animal models.	Human data in pregnancy sparse; potential concerns with endocrine interaction.
Flavonoids in general (e.g., quercetin)	Moderate inhibition of MMPs, reduce inflammatory cytokines.	Likely safe in dietary amounts; medicinal high doses need evaluation.

- Some medicinal plants traditionally used for uterine tonics or to delay labor may have effects on ECM or hormone modulation; for example, plants with tannins or saponins that tighten connective tissue or reduce protease activity. But no definitive studies showing effect on relaxin.

Gaps in Knowledge

- Lack of direct studies (in vitro, animal or human) showing that medicinal plants reduce relaxin expression or activity.
- Lack of safety and dosage studies of such plants or compounds in pregnancy.
- Potential off-target effects on other hormones or fetal development.
- Interactions between plant compounds and usual pregnancy physiology.

Discussion: Relaxin plays a significant role in preterm birth mechanisms by remodeling cervical ECM, increasing MMP activity, softening the cervix, increasing risk of PPROM. If one could modulate relaxin (either reduce its overexpression, or block its downstream effects), one might reduce preterm birth risk. Although there is no direct

evidence yet of medicinal plants modulating relaxin, the known activities of several phytochemicals on MMPs, inflammation, oxidative stress suggest plausible mechanisms. These could serve as indirect control of adverse relaxin effects. However, pregnancy is a delicate state; any intervention must be rigorously evaluated for safety, especially in the first trimester and regarding effects on fetal development, hormonal balance, placenta.

Proposed Strategies for Improvement / Research

1. **In vitro screening:** Use human decidua, fetal membrane/cervical tissue culture to test various plant extracts / compounds for effects on relaxin gene expression, receptor expression (RXFP1, LGR7), MMP/TIMP balance.
2. **Animal models:** pregnant animal models to test efficacy and safety: whether plant extracts administered during gestation modulate serum relaxin, cervical remodeling, gestational length.
3. **Dose-finding and toxicity studies:** Identify safe dosage ranges, avoid teratogenicity, ensure no negative impact on maternal or fetal health.
4. **Pilot human clinical trials:** small scale, with close monitoring, of plant-based interventions (or purified compounds) in women at high risk for preterm birth, measuring relaxin levels, biomarkers of ECM remodeling, cervical length, pregnancy outcome.
5. **Standardisation of plant preparations:** consistency in active ingredient content, purity, dosing; ensure regulatory oversight.
6. **Mechanistic studies:** identify precisely how plants or compounds may suppress relaxin: via lowering production (e.g. via luteal function), receptor antagonism, or via downstream inhibition of relaxin effects (MMPs, inflammation).

Proposed Conceptual Diagram (see Figure)

- Figure A: Pathway of Relaxin in pregnancy → increased relaxin leads to cervical softening / increased MMPs / ECM remodelling → PPROM / preterm birth risk.
- Figure B: Proposed points of plant-based intervention: block relaxin gene expression; block receptor activation; inhibit MMPs; reduce oxidative stress/inflammation; strengthen ECM.

Ethical and Practical Considerations

- Safety is paramount: plant compounds may have hormonal side effects, or unknown teratogenic effects. Must comply with ethical standards.
- Regulatory issues: medicinal plant use in pregnancy is often under-regulated.
- Cultural acceptance: use of medicinal plants may vary; acceptability and access matter.
- Standardization and quality control of plant extracts are critical.

Conclusion: The evidence supports relaxin as a contributory factor to preterm birth via effects on cervical remodeling, extracellular matrix breakdown, and PPROM. While direct evidence for medicinal plants modulating relaxin is currently lacking, indirect data (on MMPs, inflammation, oxidative stress) provide a plausible basis for exploring plant-based interventions. Future research, starting from in vitro work, through animal

models, to carefully designed human trials, is needed. Proper safety evaluation, dosage standardization, and ethical oversight will be essential. If successful, medicinal plants could provide an accessible, cost-effective adjunctive strategy to reduce preterm birth risk in at-risk pregnant women.

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