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Review Article

Oxidative Stress Modulation in Chronic Rhinosinusitis with Nasal Polyps: Mechanistic Perspectives on *Teucrium marum* Varum

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ABSTRACT

It is becoming more well recognized that Chronic Rhinosinusitis with Nasal Polyps (CRSwNP) is a self-sustaining mucosal ecosystem in which oxidant-antioxidant imbalance, microbial dysbiosis, stromal remodeling, type 2 immunological polarization, and epithelial damage support each other. This paper critically summarizes redox dysregulation in CRSwNP and assesses whether *Teucrium marum* Varum (TMV), a Mediterranean Lamiaceae taxon rich in terpenoids, provides a physiologically feasible pathway to modifying this axis based on mechanistic considerations. Using a Boolean concept-block method and PRISMA-informed search and reporting framework reporting standards, an organized narrative search of PubMed, Scopus, Web of Science, and Google Scholar (2015-2026) reduced 487 de-duplicated data to 47 included sources. Quantitative analysis of tissue-biomarker and radical-scavenging data reveals quantifiable KEAP1-NRF2-HO-1 activation in CRSwNP tissue, which is still outpaced by oxidant accumulation. It also identifies TMV chemotypes enriched in (E)-β-caryophyllene and dolichodial as mechanistically, but not directly, convergent on this deficit. There are no CRSwNP-specific data available for *T. marum* varum. The next phase is not empirical application, but rather chemotype-standardized, biomarker-anchored preclinical testing.

Keywords: Chronic Rhinosinusitis with Nasal Polyps, Nrf2-Keap1 signalling, Oxidative Stress, Phytochemical antioxidants, *Teucrium marum*, β-caryophyllene.

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INTRODUCTION

One of the most debilitating inflammatory conditions of the upper respiratory tract is chronic rhinosinusitis with nasal polyps, which combines chronic symptoms, poor smell, asthma comorbidity, and a significant risk of return following surgery or corticosteroid cessation. (Nappi *et al*., 2025). Although endoscopic surgery and biologics that target IL-4Rα, IL-5, or IgE have improved care, many patients still go through cycles of topical steroids, systemic rescue treatment, and repeat procedures. This indicates that CRSwNP is caused by self-organization of a diseased mucosal niche rather than a single mediator (Nappi *et al*., 2025; He *et al*., 2023). Oxidant-antioxidant imbalance is a consequential and relatively under-targeted axis among the mechanisms supporting this niche: reactive oxygen species produced by epithelial injury, pollutant exposure, inflammatory cells, and microbial interaction damage membranes, proteins, and DNA while also acting as second messengers that intensify NF-κB-dependent inflammatory transcription, correlating with tissue eosinophilia, mucosal damage, and poor response to treatment (Tai *et al*., 2023).

This review is motivated by three factors. First, because oxidative stress occurs concurrently upstream and downstream of epithelial barrier failure, type 2 amplification, and stromal remodeling rather than as a separate process, redox biology serves as a mechanistically unifying lens (Tai *et al*., 2023; Bachert *et al*., 2024). Second, since phytochemicals can operate on several converging antioxidant and anti-inflammatory nodes simultaneously-a polypharmacological feature appropriate for a disease characterized by network dysregulation rather than a single druggable target-interest in plant-derived redox modulators has resurfaced (Gagliano *et al*., 2021). Third, *T. marum* varum, a Mediterranean Lamiaceae taxon with an exceptionally rich volatile chemistry, has never before been systematically assessed against the CRSwNP oxidative-stress literature (Maccioni *et al*., 2023).

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The objectives of this review are to: (i) describe the oxidant-antioxidant circuitry in CRSwNP, with a focus on the KEAP1-NRF2-HO-1 axis and its interaction with NF-κB/MAPK signaling; (ii) summarize the phytochemistry of *Teucrium marum* Varum (TMV) that is relevant to antioxidants; (iii) critically map the degree of mechanistic convergence between the two literatures rather than describing them side by side. The search strategy is described in Section 2; oxidative stress in CRSwNP is discussed in Section 3; TMV phytochemistry is reviewed in Section 4; the critical mechanistic synthesis is carried out in Section 5; formulation implications are discussed in Section 6; limitations and future priorities are outlined in Sections 7-8; and the conclusion is given in Section 9.

LITERATURE SEARCH METHODOLOGY

The PRISMA-informed search and reporting strategy guided the search, screening, and reporting of this structured narrative (non-systematic) review. statement when appropriate. Because the goal was critical mechanistic mapping across two different literatures rather than pooled quantitative synthesis of a single homogeneous question, two deviations from the full systematic-review methodology are explicitly stated: screening was carried out by a single reviewer team without a second independent screener, and no protocol was prospectively registered. These deviations are reviewed in Section 7.

Three PICO-adapted concept blocks were created from the search terms: Block A, disease/tissue context (CRSwNP); Block B, redox mechanism (oxidative stress, KEAP1-NRF2-HO-1, NF-κB/MAPK); and Block C, possible phytochemical exposure (Teucrium marum, related terpenoids). Boolean while was used to join blocks, while Boolean OR and truncation were used to mix synonyms within each block (e.g., "oxidant," "polyp"). This review's critical-synthesis method was motivated by the lack of direct disease-specific data, which was confirmed by running a third combination (A AND C). The precise syntax is replicated in Table 1.

Records published between January 2015 and June 2026 were located by searching PubMed/MEDLINE, Scopus, Web of Science (Core Collection), and Google Scholar; older fundamental articles were only included if they were load-bearing for a referenced mechanism (e.g., seminal KEAP1-NRF2-ARE descriptions). For more relevant primary research, the reference lists of the included reviews were manually searched.

Peer-reviewed original research, mechanistic/experimental studies, systematic reviews, or narrative reviews published in English between January 2015 and June 2026 (or earlier if foundational) that directly addressed oxidative stress/redox signaling in CRSwNP, Teucrium/Lamiaceae phytochemistry, or cross-system β-caryophyllene/terpenoids/iridoid pharmacology were all eligible. Conference abstracts, non-peer-reviewed preprints, sources without traceable methodology, duplicate reports of the same dataset (most recent/complete version retained), case reports without mechanistic or phytochemical data, records unrelated to redox biology or Teucrium/terpenoids pharmacology on full-text review, and non-English full texts without translation were all excluded.

The entire texts of possibly eligible records were independently reevaluated using the same criteria after the records were de-duplicated and screened at the title/abstract level. This procedure is shown in Figure 1 as a flow diagram inspired by PRISMA 2020. Cross-system and genus-level data was purposefully kept for Blocks B and C and is marked as such throughout because there are no clinical or CRSwNP-specific preclinical investigations of TMV. This heterogeneous collection was not subjected to a formal risk-of-bias instrument (such as SYRCLE or ROBINS-I); instead, each source's model system is provided inline, and Section 5 makes explicit the aggregate evidential weight.

Oxidative Stress in CRSwNP: The Central Disease Axis

Due to its enormous surface area, constant aerobic metabolic demand, and direct interaction with contaminants and microbial metabolites, the respiratory epithelium is disproportionately exposed to oxidative stress. Tight-junction loss, protease exposure, and persistent immune infiltration exacerbate this susceptibility in CRSwNP, producing reactive oxygen/nitrogen species that harm epithelial membranes and increase NF-κβ-dependent transcription of alarmins and type 2 cytokines (Tai et al., 2023). Tissue-level research has revealed elevated NOS2/NOX1 along with HO-1 and SOD2 in macrophages and epithelial cells. Oxidase levels are positively correlated with IL-5/IL-6 and antioxidant enzyme levels are inversely correlated with IL-13/interferon-γ, a pattern that is consistent with KEAP1-NRF2 activation but is insufficient to counteract oxidant accumulation (Zhou *et al*., 2024). The primary lesion that every redox-directed remedy has to treat is this "compensatory but overwhelmed" hallmark Figure 2.

The primary regulator of this response is NRF2, which is sequestered by KEAP1 under baseline circumstances. Oxidative/electrophilic stress breaks this complex, enabling nuclear translocation and ARE-dependent transcription of HO-1, SOD, catalase, glutathione peroxidase, and NQO1 (Zhou *et al*., 2024; Ramanathan *et al*., 2021). In a papain-induced eosinophilic rhinosinusitis paradigm, mice missing epithelial Nrf2 exhibit much higher goblet-cell hyperplasia, tissue eosinophilia, and mucosal IL-13. This suggests that NRF2 responsiveness is a factor in susceptibility rather than a bystander (Ramanathan *et al*., 2021). Following exposure to particulate matter and cigarette smoke, NRF2 activation also restores the integrity of the nasal epithelial barrier, mechanistically connecting redox signaling to the barrier deficiencies that start the wider cascade (Tai *et al*., 2023).

Crucially, NRF2 activation reduces NF-κβ-driven transcription, whereas unresolved oxidative stress promotes nuclear NF-κβ translocation and the release of TSLP, IL-25, IL-33, and the IL-4/IL-5/IL-13 cluster that defines type 2 CRSwNP. This reciprocal antagonistic relationship between KEAP1-NRF2-ARE and NF-κβ and its upstream MAPK regulators (Tai *et al*., 2023; Zhou *et al*., 2024). This explains why oxidative stress is not a fortuitous discovery but rather acts as a disease amplifier. Principal mediators are summarized in Table 2.

The causal argument that NRF2 responsiveness affects susceptibility is based on a murine knockout model, whereas tissue-level oxidase/antioxidant correlations are cross-sectional human data (Zhou *et al*., 2024). It is crucial to distinguish between these forms of evidence rather than confusing them (Ramanathan *et al*., 2021). The murine model raises questions about whether epithelial-Nrf2 dependency extends to polymicrobial, chronically remodeled human tissue, and cross-sectional data cannot determine whether HO-1/SOD2 elevation is compensatory or independently contributory. The two threads are complimentary rather than redundant, and neither one by itself can sustain the strength of assertion that their combination may suggest.

Phytochemistry of TMV

TMV is known for its abundance of chemicals, including terpenoids, diterpenoid scaffolds, and essential oils. A recent genus-level synthesis that emphasizes pharmacologically intriguing mixtures of terpenoids, phenolics, and iridoid-related metabolites rather than a single dominant constituent supports a genus-wide review that identified a variety of volatile metabolites with antimicrobial, anti-inflammatory, and antioxidant relevance across taxa. Ten For a polyfactorial disease like CRSwNP, where a single molecular target is probably insufficient, this chemical plurality is important.

The chemotaxonomic profile of TMV is unique. Dolichodial and (E)-β-caryophyllene were found to be the most prevalent phytochemicals in a 2023 population study conducted across Sardinian habitats. Dolichodial enrichment was higher in coastal populations, while (E)-β-caryophyllene abundance was higher in mountain populations. These findings were explained by differences in insect pressure, drought stress, and microbial risk. Therefore, unless chemotype, location, and extraction technique are regulated, crude formulations are unlikely to behave as chemically homogeneous therapies.

The most well-characterized component related to CRSwNP redox biology is β-caryophyllene. It functions as a selective CB2 agonist with downstream anti-inflammatory, antioxidant, and NF-κβ-suppressive actions, according to a molecular review (Baradaran *et al*., 2022). In a rat cerebral ischaemia-reperfusion paradigm, β-caryophyllene pre-treatment directly activated the KEAP1-NRF2-HO-1 pathway, as demonstrated by decreased lipid peroxidation and malondialdehyde and increased SOD and catalase activity (Lou *et al*., 2016). Although these findings are not generated from airways or CRSwNP, they demonstrate that the antioxidant mechanism of β-caryophyllene functions via the same NRF2-HO-1/NF-κβ circuit that is important to Section 3, which serves as the foundation for the mechanistic, not evidential, convergence suggested here.

This chemical class is quantitatively supported by direct antioxidant test data. In addition to cyclooxygenase-inhibitory and cytotoxic action, *Teucrium pruinosum* essential oil showed concentration-dependent DPPH radical-scavenging activity with IC_{50} = 16.98 ± 0.84 μg/mL against a Trolox reference of 2.09 ± 0.17 μg/mL (Jaradat *et al*., 2018). Other *Teucrium* species have been observed to have comparable DPPH/FRAP activity (Figure 3), which often correlates with overall phenolic and terpenoid content. The main phytoconstituents are shown in Table 3.

There is internal heterogeneity in this literature. Since DPPH and FRAP use different reference standards, measure similar but different aspects of radical scavenging, and are rarely cross-reported for the same extract, it is impossible to directly compare IC_{50} values (Jaradat *et al*., 2018). With FRAP-based potency from other species without a shared analytical standard. This is a comparability gap rather than just a data gap. Chemotype variability exacerbates this: potency data from unidentified

Table 1: Boolean search concept blocks (PICO-adapted) and representative database syntax.

Concept block	Key terms (OR-combined; truncated)	Example syntax
A - Disease/tissue context	"CRSwNP"; "nasal polyp*"; "chronic rhinosinusitis"	PubMed: ("nasal polyps"[MeSH] OR "chronic rhinosinusitis" [tiab] OR CRSwNP [tiab])
B - Redox mechanism	"Oxidative stress"; "oxidant*"; "Nrf2"; "KEAP1"; "HO-1"; "SOD"; "NF-κβ"; "MAPK"	Scopus: TITLE-ABS-KEY ("oxidative stress" OR Nrf2 OR KEAP1 OR "NF-kappa β")
C - Phytochemical/taxon exposure	"*Teucrium marum*"; "Lamiaceae"; "β-caryophyllene"; "dolichodial"; "DPPH"; "FRAP"	Web of Science: TS= (Teucrium OR "beta-caryophyllene" OR dolichodial) AND TS= (antioxidant* OR DPPH OR FRAP)
Combinations run	A AND B; C AND (B-antioxidant terms); A AND C (direct-evidence check)	Boolean AND across blocks; OR/truncation within blocks; A AND C confirmed the evidence gap

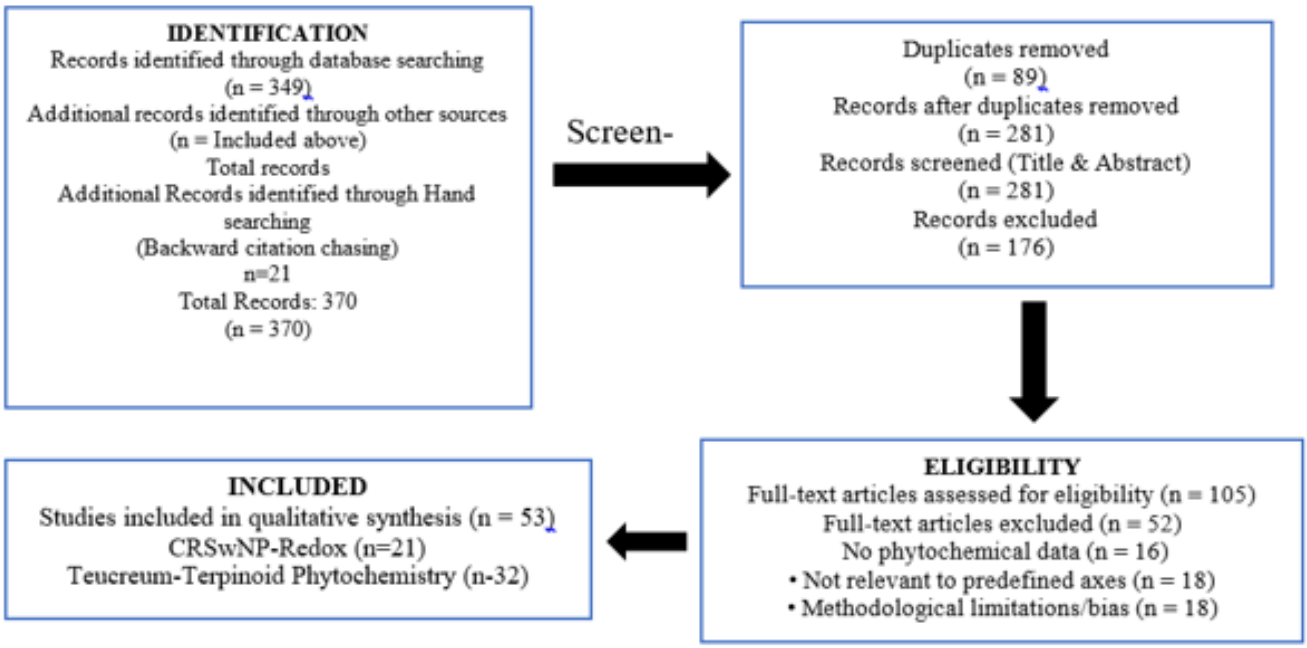

Figure 1: PRISMA-informed search and reporting framework of literature identification, screening and inclusion (Section 2). Screening was performed by a single reviewer team without duplicate independent screening or prospective registration.

or pooled sources cannot be believed to be generalizable to a chemotype-defined preparation since dolichodial- and β-caryophyllene-dominant TMV populations differ systematically by location. Lastly, mechanistic (KEAP1-NRF2-HO-1) No single study links a chemotype-defined TMV fraction to both endpoints at the same time because the phenomenological (DPPH/FRAP) antioxidant literatures have developed largely in parallel, with pathway data almost exclusively for isolated β-caryophyllene (Lou *et al.*, 2016). And scavenging data almost exclusively for whole essential oils (Jaradat *et al.*, 2018). The main evidential flaw found here is this fragmentation rather than direct dispute.

Evidence Hierarchy and Translational Interpretation Framework

The lack of disease-specific experimental or clinical data is one of the main obstacles in assessing the therapeutic potential of TMV in Chronic Rhinosinusitis with Nasal Polyps (CRSwNP). As a result, this review uses a translational evidence approach to separate proven biological data from mechanistic plausibility rather than inferring therapeutic efficacy. This method minimizes the exaggeration of indirect findings while allowing a fair evaluation of the existing literature.

According to the use of this methodology, Level III and Level IV evidence are the main sources of support for the suggested link between TMV and Chronic Rhinosinusitis with Nasal Polyps (CRSwNP). There is presently no experimental or clinical evidence unique to CRSwNP, despite the fact that β-caryophyllene and other TMV phytochemicals show antioxidant action in Teucrium species and alter NRF2-KEAP1/HO-1 and NF-κB signaling in non-airway models. Therefore, rather than supporting treatment effectiveness, the observed mechanistic convergence supports biological plausibility. Prior to clinical translation, future research should confirm these results utilizing chemotype-standardized TMV formulations in disease-specific experimental models.

The recovered evidence was categorized into four hierarchical tiers in order to increase transparency. based on how relevant it is to CRSwNP (Table 4). Phytochemical characterisation and general antioxidant research are included in Level IV; airway-specific experimental studies are included in Level II; mechanistic studies of TMV phytoconstituents in non-airway models are included in Level III; and direct CRSwNP experiments employing TMV are included in Level I. This concept highlights that rather than disease-specific treatment effectiveness, the evidence currently available mostly supports mechanistic plausibility.

Critical Synthesis: Mechanistic Intersections and Evidence Strength

The more persuasive analytical job is to critically map which CRSwNP disease modules its chemistry may realistically affect and with what degree of proof, rather than asking whether TMV "treats" nasal polyps in a binary sense. There are five potential crossings that are assessed comparatively rather than descriptively.

Oxidative stress itself is the strongest and most obvious intersection. Epithelial NRF2 depletion directly exacerbates eosinophilic inflammation in experiments, and CRSwNP tissue has a measurable KEAP1-NRF2-HO-1 activation signature driven by oxidant buildup (Zhou *et al.*, 2024; Ramanathan *et al.*, 2021). In cross-system pharmacology, β-Caryophyllene-enriched chemotypes converge on exactly this axis; genus-level DPPH data verify quantifiable scavenging ability (Jaradat *et al.*, 2018). An

end-to-end mechanism-matched evidence chain only exists for this junction (Figure 4).

Since cytokine exposure and oxidative damage destabilize the CRSwNP epithelium, a phytochemical mixture that reduces oxidative burden and NF-κβ transcription may indirectly restore junctional competence and lower TSLP/IL-25/IL-33 release (He et al., 2023; Bachert et al., 2024). However, no study has tested TMV against barrier readouts, so this remains an inference rather than a proven effect.

A third, weaker intersection is type 2 immune amplification: mast cells amplify through CRTH2-dependent ILC2 activation, while IL-4/IL-13 promote eosinophilic recruitment and periostin induction (Bachert *et al.*, 2024; Locatello *et al.*, 2024). Teucrium would have an indirect effect in this case through decreased activation of mast cells and macrophages as a result of decreased oxidative/NF-κβ drive.

The weakest intersection is stromal remodeling. CRSwNP tissue exhibits periostin-rich matrix growth fueled by coagulation and matrix metalloproteinases, fibrin retention, and factor XIIIa-mediated stabilization (Amirapu *et al.*, 2021; Cao *et al.*, 2022; Abdullah *et al.*, 2026). There is no direct or cross-system evidence connecting TMV to periostin regulation or fibroblast activation; this relationship is still hypothetical.

Microbial/biofilm persistence occupies an intermediate position: recent CRS models highlight dysbiosis as a co-driver rather than merely a consequence of chronicity, while genus-level antimicrobial activity is relatively well documented (Gagliano Candela *et al.*, 2021; Kimta *et al.*, 2026) and ecological evidence links *T. marum* chemistry to defensive adaptation against microbial/insect threats (Maccioni *et al.*, 2023; Petalas and Konstantinou, 2026; Broderick *et al.*, 2025). Although formulation-constrained, this is physiologically significant since concentrations high enough to impact biofilms run the risk of irritating already damaged epithelium.

In lieu of a traditional meta-analytic forest plot, Figure 5 shows a radar/pentagon comparison of the two main chemotypes across five redox-relevant domains, and Figure 6 shows a quantitative scatter of evidence-strength tiers against number of supporting sources per intersection. Pooled effect sizes cannot be legitimately computed because there are no comparable quantitative CRSwNP-specific trials of TMV, and creating them would misrepresent the field's evidentiary state. This classification is reiterated in Table 5 with source attribution: oxidative stress consistently has the most evidence, whereas stromal remodeling has the weakest.

Therapeutic Implications and Formulation Logic

The mode of administration is just as important as chemistry if TMV is to be translated meaningfully. Topical delivery using irrigation-compatible emulsions, gels, or nanoparticle-assisted sprays is more sensible because it targets the diseased epithelial

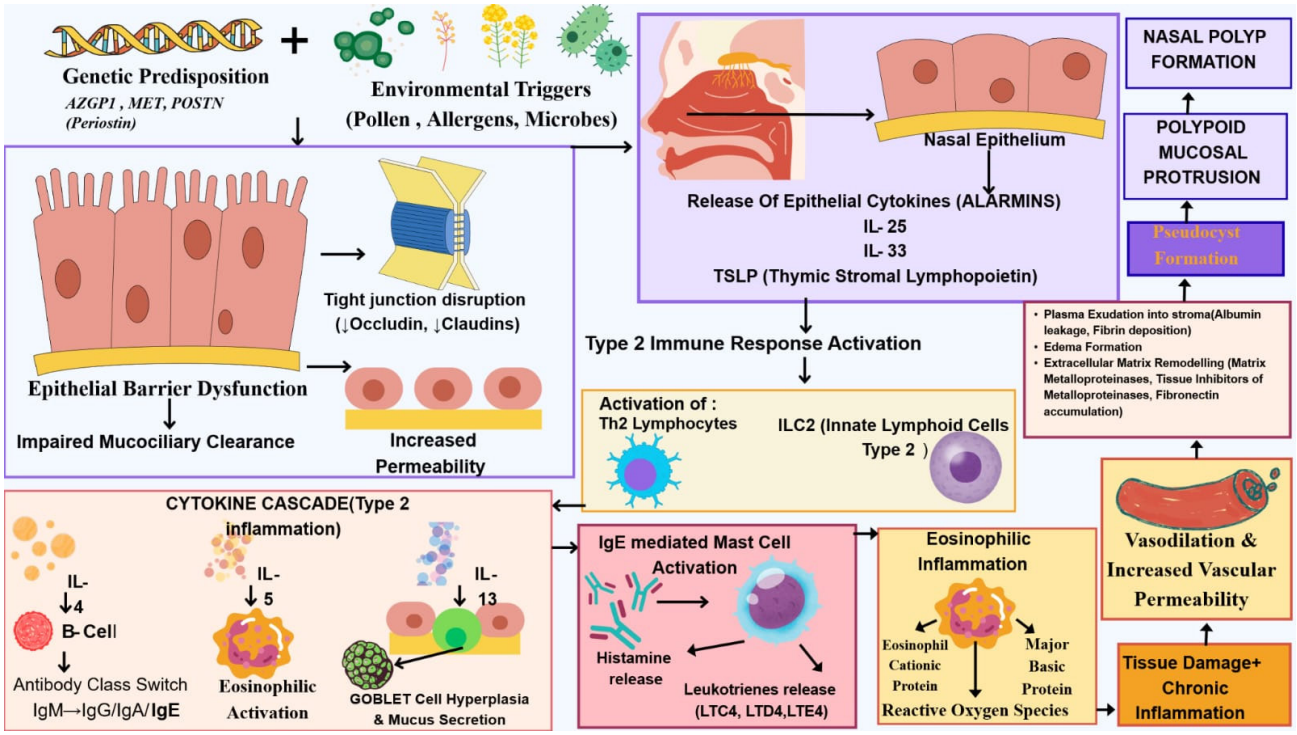

Figure 2: Overview of the nasal polyp tissue microenvironment as an interconnected pathobiological network, integrating genetic predisposition, epithelial barrier dysfunction, alarmin release, type 2 immune activation, cytokine cascades, coagulation/matrix changes and polyp formation. Positioned at the opening of Section 3 to establish the systems-level context within which the oxidative-stress axis discussed in this review operates.

Table 2: Oxidative stress mediators and biomarkers implicated in CRSwNP.

Mediator/Biomarker	Type	Reported role in CRSwNP	Source
NOX1 / NOS2	Pro-oxidant enzymes	Up-regulated in polyp epithelium/macrophages; correlates positively with IL-5, IL-6	(Zhou *et al.*, 2024)
HO-1	Antioxidant (NRF2-ARE target)	Increased in polyp tissue but insufficient to offset oxidant burden	(Tai *et al.*, 2023; Zhou *et al.*, 2024)
SOD2	Antioxidant enzyme	Increased in polyp tissue; inversely correlated with IL-13, IFN-γ	(Zhou *et al.*, 2024)
Catalase / GPx / NQO1	Antioxidant enzymes	Components of the ARE-driven cytoprotective response	(Tai *et al.*, 2023; Zhou *et al.*, 2024; Ramanathan *et al.*, 2021)
NRF2 (nuclear translocation)	Master transcription factor	Epithelial loss worsens eosinophilia and IL-13 in a murine model	(Ramanathan *et al.*, 2021)
NF-κB (nuclear localization)	Pro-inflammatory transcription factor	Reciprocal antagonist of NRF2; drives TSLP/IL-25/IL-33 and type-2 cytokines	(Tai *et al.*, 2023; Zhou *et al.*, 2024)
MDA / lipid peroxidation	Oxidative damage marker	General marker of airway oxidative injury across the CRS literature	(Tai *et al.*, 2023; Lou *et al.*, 2016)
Periostin	Matrix/structural marker	Downstream of IL-13 and oxidative-inflammatory crosstalk	(Abdullah *et al.*, 2026)

Table 3: Antioxidant-relevant phytochemicals of TMV and related Teucrium taxa.

Constituent	Chemotype/source	Reported antioxidant/redox activity	Source
(E)-β-caryophyllene	Mountain *T. marum* (Sardinia); widespread across genus	CB2-mediated anti-inflammatory action; activates KEAP1-NRF2-HO-1 in cross-system pharmacology	(Maccioni *et al.*, 2023; Baradaran *et al.*, 2022; Lou *et al.*, 2016)
Dolichodial	Coastal *T. marum* (Sardinia)	Iridoid monoterpene linked to antimicrobial/defensive function; direct antioxidant assay data not yet reported	(Maccioni *et al.*, 2023)
Whole essential oil (e.g., *T. pruinosum*)	Multiple Teucrium species	DPPH $IC_{50} \approx 17$ μg/mL; cyclooxygenase-inhibitory activity	(Jaradat *et al.*, 2018)
Phenolic/terpenoid mixture (genus-level)	*Teucrium* spp.	Antimicrobial, anti-inflammatory and antioxidant activity broadly reported across the genus	(Gagliano et al., 2021; Kimta et al., 2026)

Table 4: Translational evidence hierarchy applied in the present review.

Evidence Level	Type of Evidence	Current Availability	Interpretation
Level I	Clinical or experimental CRSwNP studies evaluating TMV	None identified	No direct evidence currently exists.
Level II	Airway-specific *in vivo* or *in vitro* studies using TMV	None identified	Disease-specific biological activity remains unknown.
Level III	Mechanistic studies of TMV phytoconstituents (e.g., β-caryophyllene) in non-airway inflammatory or oxidative stress models	Available	Supports biological plausibility but not disease-specific efficacy.
Level IV	General phytochemical characterization, antioxidant assays (DPPH, FRAP), and genus-level pharmacological studies	Available	Demonstrates antioxidant potential but cannot predict clinical effectiveness.

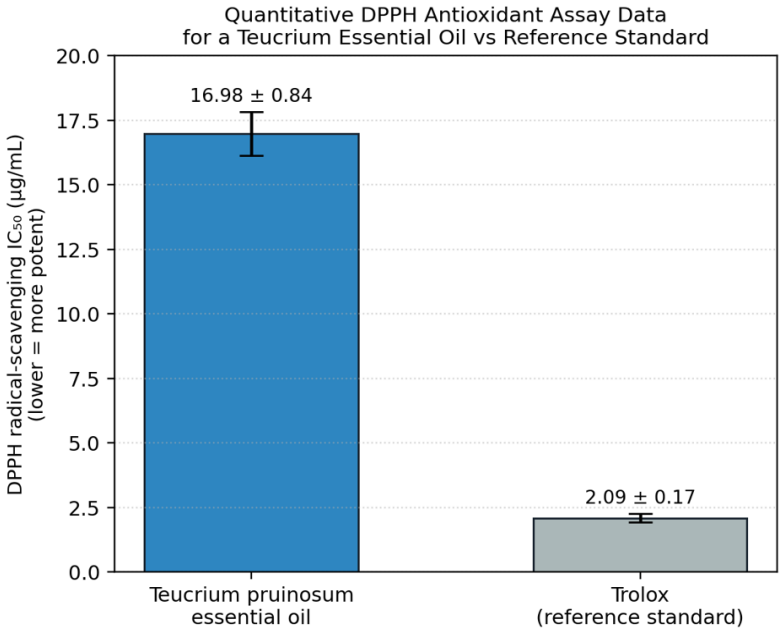

Figure 3: Quantitative DPPH radical-scavenging IC_{50} (µg/mL, Mean ± SD) for *T. pruinosum* essential oil versus the Trolox reference standard (Jaradat *et al.*, 2018). Lower values indicate greater scavenging potency.

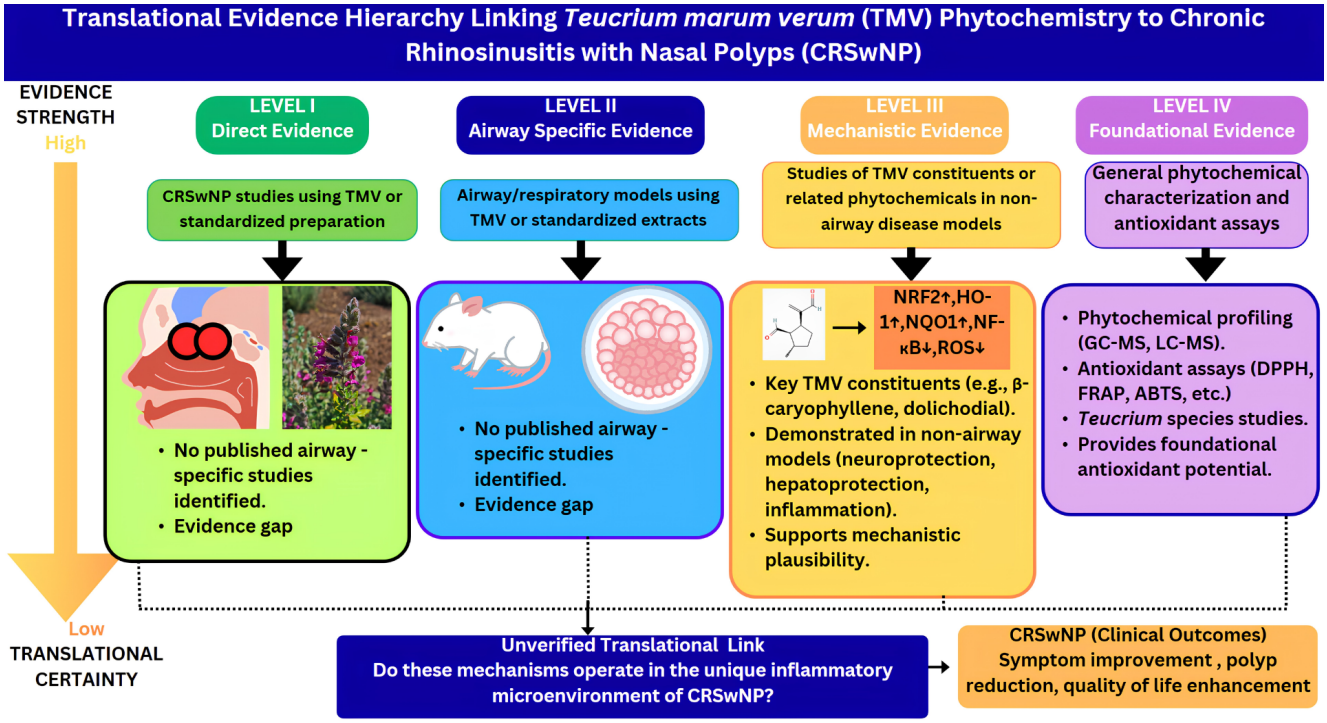

Figure 4: Translational evidence hierarchy linking TMV phytochemistry to Chronic Rhinosinusitis with Nasal Polyps (CRSwNP). The figure illustrates the progressive reduction in evidentiary strength from direct disease-specific evidence (Level I) to general phytochemical and antioxidant evidence (Level IV). Solid arrows represent experimentally demonstrated relationships, whereas dashed arrows indicate biologically plausible but unverified translational links. The framework emphasizes that current evidence supports mechanistic plausibility rather than therapeutic efficacy. Abbreviation: ROS (Reactive Oxygen Species).

surface directly, which is the same compartment where barrier failure and oxidative injury are initiated. Oral delivery exposes constituents to first-pass metabolism, making sinonasal target concentrations unpredictable (He *et al.*, 2023). This is consistent with the present treatment of CRSwNP, where saline irrigations and topical corticosteroids continue to be fundamental even in the biologic age (Nappi *et al.*, 2025).

The therapeutic window for essential oil pharmacology is limited because components that are membrane-active enough to influence bacteria may also change epithelial membranes or cause

Table 5: Evidence-level classification of the five proposed mechanistic intersections.

Disease module	Evidence tier (0-4)	Basis	Source
Oxidative stress (NRF2-KEAP1/NF-κB)	2-3	CRSwNP tissue redox data + cross-system β-caryophyllene Nrf2/HO-1 pharmacology + genus-level DPPH assays	(Tai *et al.*, 2023; Zhou *et al.*, 2024; Ramanathan *et al.*, 2021; Lou *et al.*, 2016; Jaradat *et al.*, 2018)
Microbial/biofilm persistence	1-3	Ecological defensive chemistry of *T. marum* + genus-level antimicrobial data; no CRSwNP-specific testing	(Maccioni *et al.*, 2023; Petalas and Konstantinou, 2026; Broderick *et al.*, 2025)
Epithelial barrier/alarmin signalling	1-2	Mechanistic inference from the redox-barrier link; no direct TMV testing	(He *et al.*, 2023; Bachert *et al.*, 2024)
Type 2 immune amplification	1-2	Indirect route via oxidative/NF-κB suppression; no direct receptor-level activity shown	(Bachert *et al.*, 2024; Locatello *et al.*, 2024)
Stromal/matrix remodelling	0-1	No direct or cross-system evidence identified for this module	(Amirapu *et al.*, 2021; Cao *et al.*, 2022; Abdullah *et al.*, 2026)

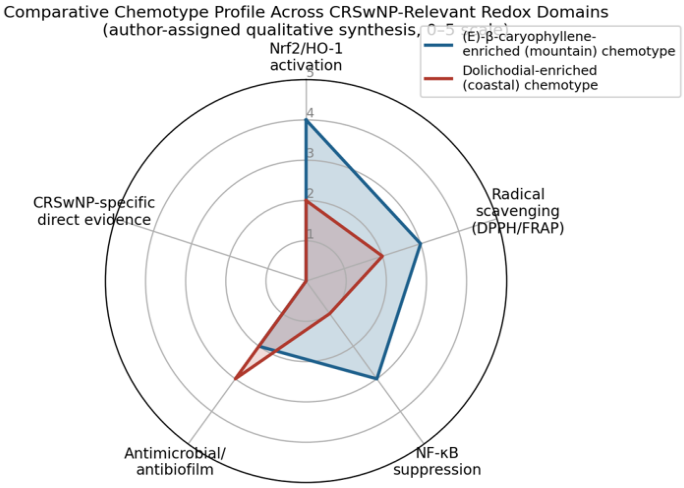

Figure 5: Radar/pentagon comparison of the two principal *T. marum* varum chemotypes across five CRSwNP-relevant redox domains. Scores (0-5) are an author-assigned literature synthesis, not measured experimental values (see Section 7).

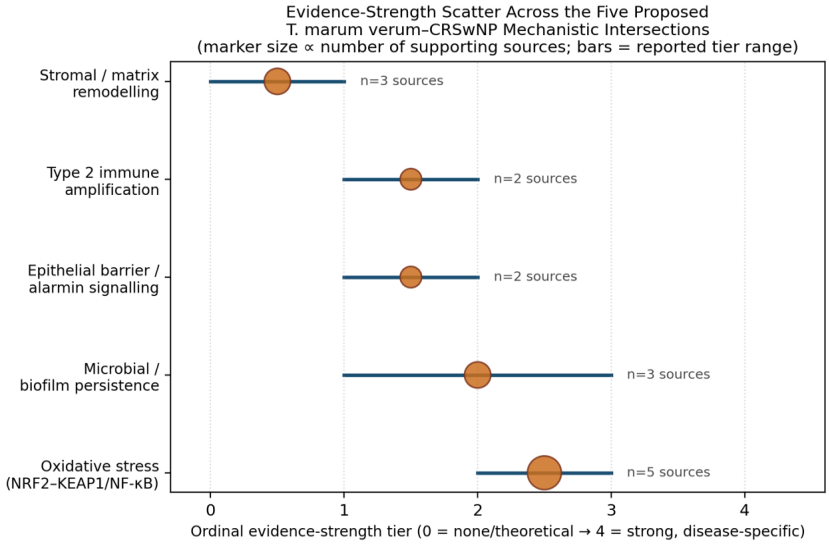

Figure 6: Evidence-strength scatter across the five proposed *T. marum* varum-CRSwNP mechanistic intersections. Marker size is proportional to the number of supporting sources; horizontal bars show the reported ordinal tier range (0 = none/theoretical to 4 = strong, disease-specific).

neurogenic irritation if they are not properly titrated. This risk is increased in situations where mucociliary clearance is already impaired (He *et al.*, 2023). Rather than crude aromatherapy-style exposure, the translational goal should be pharmacotechnical refinement-low-irritancy, chemotype-standardized fractions, plausibly enriched for the β-caryophyllene chemotype given its Nrf2/HO-1-linked mechanism-delivered via slow-release, mucosa-compatible carriers.

A phyto-molecular adjunct that slightly improves oxidative balance could theoretically supplement rather than compete with current treatment because biologics target dominant type 2 pathways without directly normalizing epithelial redox stress or sterilizing biofilms (Nappi *et al.*, 2025; Bachert *et al.*, 2024). The most significant methodological step toward bridging the Section 5 evidence gap would be biomarker-linked development, which would track NRF2 translocation, HO-1/SOD2/catalase/GPx, malondialdehyde, and 8-isoprostane alongside TSLP/IL-33/periostin (Tai *et al.*, 2023; Zhou *et al.*, 2024; Ramanathan *et al.*, 2021), anchored to the same panel used in the CRSwNP literature (Table 6). This would enable direct rather than conceptual comparison. The recentness of the literature supporting this synthesis is shown in Figure 7: 16 out of 19 listed sources (84%) were published during the previous five years, indicating that the evidence base is current even though it is still indirect for TMV in particular.

LIMITATIONS

The suggested processes are based on indirect pharmacological evidence because there is presently no direct clinical or preclinical evidence that TMV modifies CRSwNP pathophysiology or disease-specific biomarkers (Maccioni *et al.*, 2023). In the absence of phytochemical uniformity, chemotype heterogeneity

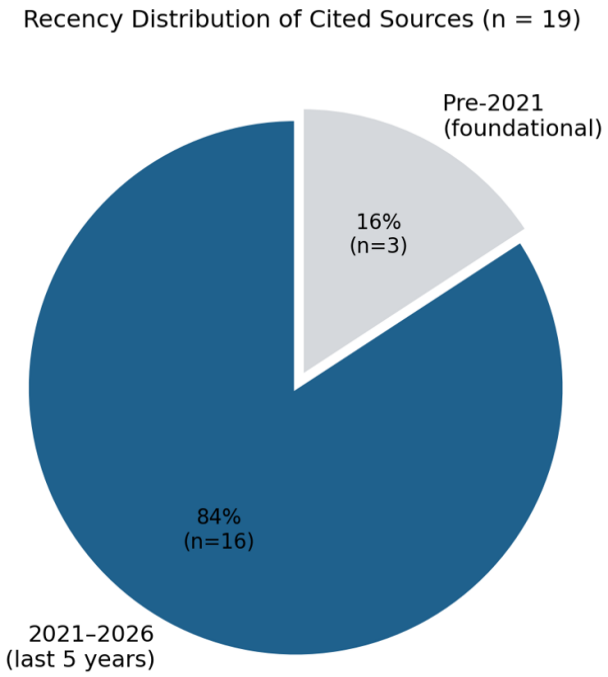

Figure 7: Recency distribution of cited sources (*n* = 19), derived from the reference list.

Table 6: Bradford Hill considerations applied to the proposed TMV-CRSwNP relationship.

Bradford Hill Criterion	Current Status	Interpretation
Biological plausibility	Supported	Shared NRF2-KEAP1/HO-1 and NF-κB pathways
Coherence	Supported	Consistent with current CRSwNP redox biology
Experimental evidence	Not established	No CRSwNP-specific TMV studies
Temporality	Not established	No longitudinal disease models
Dose-response relationship	Not established	No pharmacodynamic evidence
Consistency	Limited	Evidence derived from non-airway models
Clinical verification	Absent	No human studies available

further restricts repeatability. Furthermore, the conceptual figures in this narrative review are author-derived syntheses rather than quantitative analyses, and there was no rigorous risk-of-bias evaluation or independent screening. Lastly, there is still uncertainty regarding the mucosal safety and acceptability of TMV preparations in CRSwNP.

Despite being physiologically feasible, the suggested TMV-CRSwNP relationship does not prove therapeutic causation. According to the Bradford Hill framework, common NRF2-KEAP1/HO-1 and NF-κB pathways provide biological plausibility and coherence, but there is still a lack of experimental evidence, timing, dose-response relationship, consistency, and clinical validation. The requirement for disease-specific experimental validation prior to clinical translation is highlighted by the fact that the available evidence should be viewed as hypothesis-generating rather than evidence-confirming.

FUTURE RESEARCH DIRECTIONS

Future studies should employ a sequential translational approach, starting with *in vitro* investigations to assess inflammatory biomarkers, NRF2 activation, and epithelial barrier integrity. Then, fibroblast-immune cell co-culture models should be used to study tissue remodeling. Future research should evaluate antibacterial and anti-biofilm action against clinically significant sinonasal infections and confirm results in animal or nasal organoid models specific to the condition. To guarantee repeatability and enable future clinical translation, concurrent chemotype standardization and safety evaluations will be crucial.

CONCLUSION

The KEAP1-NRF2-HO-1 pathway is a crucial regulator of redox homeostasis in Chronic Rhinosinusitis with Nasal Polyps (CRSwNP), which is characterized by persistent oxidative stress, epithelial barrier failure, type 2 inflammation, and tissue remodeling. This review finds a molecular convergence between the antioxidant qualities of TMV phytochemicals, especially β-caryophyllene, and these pathogenic pathways. However, there is currently no disease-specific experimental or clinical validation in CRSwNP, and the majority of the data comes from indirect mechanistic and phytochemical research. Therefore, rather than being considered an evidence-based treatment intervention, TMV should be seen as a physiologically plausible but empirically unconfirmed possibility. To ascertain if this mechanistic plausibility may be converted into a clinically significant benefit, future research should give priority to chemotype-standardized preparations, disease-specific mechanistic investigations, pharmacological characterization, and safety evaluation.

ABBREVIATIONS

CRSwNP: Chronic Rhinosinusitis with Nasal Polyps; **TMV:** *Teucrium marum* Varum; **NRF2:** Nuclear factor erythroid 2-related factor 2; **KEAP1:** Kelch-like ECH-associated protein 1; **HO-1:** Heme oxygenase-1; **NF-κB:** Nuclear factor kappa-light-chain-enhancer of activated B cells; **MAPK:** Mitogen-activated protein kinase; **SOD:** Superoxide dismutase; **GPx:** Glutathione peroxidase; **NQO1:** NAD(P)H quinone dehydrogenase 1; **ARE:** Antioxidant Response Element; **PRISMA:** Preferred Reporting Items for Systematic Reviews and Meta-Analyses; **TSLP:** Thymic stromal lymphopoietin; **IL:** Interleukin; **NOS2:** Nitric oxide synthase 2; **NOX1:** NADPH oxidase 1; **MDA:** Malondialdehyde; **CB2:** Cannabinoid receptor type 2; **DPPH:** 2,2-diphenyl-1-picrylhydrazyl; **FRAP:** Ferric reducing antioxidant power; **ROS:** Reactive Oxygen Species; **PICO:** Population, Intervention, Comparison, and Outcome; **MeSH:** Medical Subject Headings; **tiab:** Title and Abstract; **IFN-γ:** Interferon-gamma.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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