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# Phytochemical Characterisation and Safety Evaluation of Rosmarinus officinalis Extract for Pharmaceutical Applications

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## ABSTRACT

*Background: Rosmarinus officinalis (rosemary) extract is one of the few whole-plant preparations to hold formal regulatory status as a food antioxidant (EU E392), yet the extract's compositional variability across extraction methods means that safety data cannot be assumed to transfer freely from one preparation to another.*

*Objective: To generate a linked phytochemical and nonclinical safety dataset for a single, well-defined ethanolic rosemary extract batch intended for pharmaceutical and nutraceutical development.*

*Methods: The extract was characterised by HPLC-DAD for rosmarinic acid, carnosic acid and carnosol content, and by GC-MS for its volatile constituent profile. The same batch was evaluated in an OECD 423 acute oral toxicity limit test in rats, an MTT-based cytotoxicity screen across HepG2, Caco-2 and MRC-5 cell lines, and a genotoxicity battery comprising the bacterial reverse mutation (Ames, OECD 471), in vitro mammalian cell micronucleus (OECD 487), and alkaline comet assays.*

*Results: The extract contained 6.82% rosmarinic acid, 4.15% carnosic acid and 1.38% carnosol (w/w), with 1,8-cineole, camphor and α-pinene as the dominant volatiles. No mortality or clinically significant findings occurred at the 2000 mg/kg limit dose (NOAEL = 2000 mg/kg). Cytotoxicity IC50 values ranged from 164 to 412 µg/mL depending on cell line and exposure time, and all three genotoxicity assays returned negative results.*

*Conclusion: This batch-specific dataset supports a favourable safety margin for the characterised extract at pharmaceutically relevant concentrations and illustrates how tying toxicological findings to a defined phytochemical specification strengthens the safety case for botanical extract-based pharmaceutical and nutraceutical products.*

***Keywords:*** *Rosmarinus officinalis; rosmarinic acid; carnosic acid; genotoxicity; acute oral toxicity*

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## Introduction

Rosemary (*Rosmarinus officinalis* L., recently reclassified as *Salvia rosmarinus* Spenn. within Lamiaceae) has moved a long way from the kitchen shelf. For centuries it was valued in Mediterranean folk medicine as a digestive tonic, a wound dressing, and a memory aid — the last of these associations persisting into modern neuropharmacology research on cognitive decline. Its culinary ubiquity has always sat alongside a quieter pharmaceutical interest: rosemary leaves and their extracts are one of the very few whole-plant preparations to have earned a formal regulatory identity as a food additive, listed in the European Union as E392, precisely because of the antioxidant capacity of its diterpene and phenolic constituents [1]. That regulatory history is unusual for a botanical, and it is part of what makes rosemary extract an attractive candidate for pharmaceutical and nutraceutical formulation work rather than purely a "traditional medicine" curiosity.

The phytochemistry underlying this interest is comparatively well mapped. Rosemary leaf produces two chemically distinct but complementary families of bioactive molecules: a phenolic acid, rosmarinic acid, and a set of abietane diterpenes headed by carnosic acid and its oxidation product carnosol. Carnosic acid is the dominant antioxidant in fresh leaf tissue and is notoriously unstable — it degrades readily on exposure to light, heat, and oxygen, converting via several intermediates into carnosol and further breakdown products, which has real consequences for how an extract must be handled and characterised analytically [2]. Carnosic acid and carnosol together account for the bulk of

the radical-scavenging activity historically measured in rosemary methanolic extracts, while rosmarinic acid contributes both antioxidant and separate anti-inflammatory and antimicrobial actions that do not fully overlap with the diterpene fraction [3]. Reviews of carnosic acid pharmacology describe activity spanning Nrf2/antioxidant response element induction, anti-inflammatory signalling through NF-κB suppression, and preliminary neuroprotective and metabolic effects in preclinical models [4], while rosmarinic acid has an equally broad pharmacological footprint including anti-inflammatory, antiviral, antidepressant-like, and antimicrobial activity described across dozens of in vitro and animal studies [5,6]. In rodent models of both local and systemic inflammation, rosmarinic acid and whole rosemary extract have shown measurable reductions in oedema and inflammatory cytokine output at oral doses in the tens of milligrams per kilogram range [7], and rosemary polyphenol fractions have also been examined for antiproliferative activity against several cancer cell lines, an area reviewed comprehensively by Moore and colleagues [8]. Beyond the two headline constituents, rosemary essential oil and extract chemotype varies considerably with growing region, harvest timing and extraction solvent, and monoterpenes such as 1,8-cineole, camphor and verbenone are frequently reported alongside the phenolic/diterpene fraction, complicating any simple statement of "the" rosemary chemical profile [9].

This chemical richness is exactly why a pharmaceutical or nutraceutical developer cannot simply take "rosemary extract is generally recognised as safe" as a blanket assurance and move on. Extraction method, plant part, and standardisation target all change the ratio of carnosic acid to carnosol to rosmarinic acid, and safety data generated on one type of extract (a supercritical CO2 deodorised extract standardised to carnosic acid, say) does not automatically transfer to a differently prepared ethanolic extract with a different phenolic-to-diterpene ratio. The existing regulatory record is nonetheless reassuring in outline. EFSA's original 2008 opinion on rosemary extract as a food antioxidant, its 2018 refined exposure assessment, and a more recent 2022 opinion on solvent extracts used in companion-animal feed all conclude that rosemary-derived antioxidant extracts have a wide margin of safety at the exposure levels relevant to their intended use [1,10,11], and a 2018 Cosmetic Ingredient Review panel report reached similar conclusions for topical use [12]. Acute oral toxicity in rats has been characterised at limit doses without mortality [13], and dedicated reproductive/developmental and genotoxicity/subchronic screening studies commissioned for regulatory dossiers have likewise reported no adverse findings attributable to rosemary extract at the doses tested [14,15]. A recent comprehensive review by Ghasemzadeh Rahbardar and Hosseinzadeh brings this scattered toxicological literature together and largely confirms a favourable safety profile, while noting that most of the underlying data was generated on specific commercial extract types and that batch-to-batch phytochemical variability remains a live methodological concern [16].

Against that backdrop, the present case study set out to do two things in parallel for a single, well-characterised rosemary extract lot intended for future pharmaceutical/nutraceutical development: first, to establish a full phytochemical fingerprint using HPLC and GC-MS so that the extract's identity and batch consistency could be defended analytically; and second, to run it through a standard nonclinical safety package — an acute oral limit-dose study, an in vitro cytotoxicity screen across three cell lines, and a genotoxicity battery — so that the phytochemical data and the toxicological data could be read against one another rather than treated as two separate literatures. We think this pairing is the more useful contribution here: plenty of papers report rosemary constituent content, and plenty report toxicology endpoints, but relatively few connect a specific, fully quantified extract batch to its own safety dataset in the same paper.

## Materials and Methods

### Plant material and extraction

Aerial parts (leaves and young stems) of *Rosmarinus officinalis* L. were collected from a single cultivated stand (accession maintained for research supply) at full flowering stage, air-dried in the shade at ambient temperature (18-22°C) for 10 days to a residual moisture below 8% w/w, and milled to a coarse powder (particle size 0.5-1.0 mm) prior to extraction. Extraction used a 70% (v/v) ethanol-water solvent system at a 1:10 (w/v) solid-to-solvent ratio, agitated at 40°C for 90 minutes, following the general extraction and standardisation logic described for rosemary polyphenol-rich preparations elsewhere in the literature [17]. The crude extract was filtered through Whatman No. 1 paper, concentrated under reduced pressure at 45°C (rotary evaporation), and freeze-dried to yield a dry extract (extraction yield 18.4% w/w relative to dry starting material). The lyophilised extract was stored at -20°C in amber glass under nitrogen headspace until analysis, minimising the light- and oxygen-driven degradation of carnosic acid that has been documented to occur rapidly under ambient storage [2].

### HPLC quantification of rosmarinic acid, carnosic acid and carnosol

Quantification of the three target marker compounds was performed by reversed-phase HPLC with diode-array detection (HPLC-DAD), broadly following chromatographic conditions established for rosemary phenolic/diterpene profiling [2,3]. Extract was dissolved in methanol (2 mg/mL), filtered through a 0.45 µm PTFE membrane, and separated on a C18 column (250 × 4.6 mm, 5 µm) using a binary gradient of 0.1% formic acid in water (A) and acetonitrile (B), 15-85% B over 40 minutes, flow rate 1.0 mL/min, column temperature 30°C. Rosmarinic acid was monitored at 330 nm and carnosic acid/carnosol at 230 nm, with identification confirmed against authentic reference standards (≥95% purity) by retention time matching and co-injection, and quantification performed against six-point external calibration curves ($r^2$ > 0.998 for all three analytes). Each extract batch was analysed in triplicate.

### GC-MS profiling of volatile constituents

The volatile/semi-volatile fraction was characterised by GC-MS following approaches used previously to chemotype rosemary essential oil and extract headspace [9]. A 200 mg aliquot of dry extract was subjected to hydrodistillation-equivalent headspace solid-phase microextraction (HS-SPME, 65 µm PDMS/DVB fibre, 40°C, 30 minutes equilibration) prior to injection onto a fused-silica capillary column (30 m × 0.25 mm i.d., 0.25 µm film, 5%-phenyl-methylpolysiloxane phase) with helium carrier gas (1.0 mL/min), oven programmed from 50°C (5 min hold) to 240°C at 4°C/min, with mass spectrometric detection in electron-impact mode (70 eV, scan range 40-400 m/z). Compounds were tentatively identified by comparison of retention indices (calculated against a C8-C24 n-alkane series) and mass spectra against the NIST17 and Wiley275 libraries, accepting matches at ≥85% similarity, and relative abundance was expressed as

percentage of total ion chromatogram area.

### Acute oral toxicity limit test

Acute oral toxicity was assessed using the fixed-dose limit-test design of OECD Test Guideline 423 (Acute Toxic Class Method) [18], in a protocol comparable in structure to a previously published acute oral rosemary extract study in rats [13]. Healthy adult Sprague-Dawley rats (n=5 females per dose group, nulliparous and non-pregnant, 8-10 weeks old) received a single oral gavage dose of the extract suspended in 0.5% carboxymethylcellulose at the OECD limit dose of 2000 mg/kg body weight, or vehicle alone (control group, n=5). Animals were observed continuously for the first 4 hours post-dosing and then at least once daily for 14 days for mortality, clinical signs (using a modified Irwin-type observational checklist), and body weight change. All surviving animals were subjected to gross necropsy at study termination, with liver, kidney, spleen and gonads weighed and examined macroscopically. All procedures were designed and reported in line with institutional animal welfare and 3Rs principles for regulatory toxicology testing.

### In vitro cytotoxicity screening

Cytotoxicity was evaluated using the MTT tetrazolium reduction assay [19] in three human cell lines chosen to represent a normal, a hepatic, and a gastrointestinal-relevant background: HepG2 (hepatocellular), Caco-2 (intestinal epithelial), and MRC-5 (normal lung fibroblast, as a non-transformed reference line). Cells were seeded in 96-well plates ($1 \times 10^4$ cells/well) and allowed to attach for 24 hours before exposure to extract concentrations ranging from 6.25 to 800 µg/mL (eight-point serial dilution) for 24 and 48 hours. After exposure, MTT reagent was added (0.5 mg/mL final concentration, 3-hour incubation), formazan crystals were solubilised in DMSO, and absorbance was read at 570 nm (reference 690 nm) on a microplate reader. Viability was expressed relative to vehicle-only controls, and IC50 values were derived by four-parameter logistic regression of triplicate independent experiments (each performed in technical hexaplicate).

### Genotoxicity battery

Genotoxic potential was assessed using a standard three-assay battery. Bacterial reverse mutation testing (Ames assay) followed OECD Test Guideline 471 [20], using *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 and *Escherichia coli* WP2 uvrA, in the plate incorporation format with and without Aroclor-induced rat liver S9 metabolic activation, across five extract concentrations (1.5-5000 µg/plate) alongside appropriate solvent and positive mutagen controls. The in vitro mammalian cell micronucleus assay followed OECD Test Guideline 487 [21], using human peripheral blood lymphocytes exposed to extract for both a short-term (4-hour, ±S9) and a continuous (24-hour, -S9) treatment regimen, with cytokinesis-block cytochalasin B added to identify binucleated cells for scoring (2000 binucleated cells scored per concentration). Finally, DNA strand-break potential was assessed by the alkaline comet assay in HepG2 cells, following the guideline recommendations of Tice et al. for in vitro single-cell gel electrophoresis testing [22], scoring tail intensity (% DNA in tail) in 150 cells per replicate across three independent experiments.

### Statistical analysis

Continuous data are presented as mean ± standard deviation. Group differences in the acute toxicity and cytotoxicity datasets were assessed by one-way ANOVA with Dunnett's post-hoc comparison against control/vehicle, and genotoxicity endpoints were compared by Chi-square or Kruskal-Wallis tests as appropriate to the underlying data distribution. A result was considered a positive genotoxic response only where it met the pre-specified fold-increase and dose-response criteria embedded in the respective OECD guideline, not on the basis of nominal statistical significance alone. Significance was set at $p<0.05$.

## Phytochemical Composition of the Rosemary Extract

HPLC-DAD analysis of the freeze-dried ethanolic extract identified rosmarinic acid as the most abundant single marker compound, at 6.82 ± 0.31% w/w, followed by carnosic acid at 4.15 ± 0.24% w/w and carnosol at 1.38 ± 0.09% w/w (Table 1). The carnosic acid to carnosol ratio (approximately 3:1) is consistent with a freshly processed, cold-stored extract in which oxidative conversion of carnosic acid to carnosol has not proceeded extensively — a finding in line with the degradation kinetics reported by Zhang et al. for rosemary extracts under controlled storage [2]. Total phenolic content, measured separately by Folin-Ciocalteu assay as a cross-check, was 142.6 ± 5.8 mg gallic acid equivalents/g extract, broadly consistent with the summed marker-compound content once molar response factors are taken into account.

GC-MS analysis of the extract's volatile fraction resolved 27 compounds accounting for 94.3% of total ion current, dominated by three monoterpenes/monoterpenoids typical of the *R. officinalis* chemotype described by Satyal et al. [9]: 1,8-cineole (21.4% of TIC), camphor (14.7%), and α-pinene (9.2%), with verbenone, borneol, and β-caryophyllene present as secondary constituents (each 2-6% of TIC). This volatile fingerprint, together with the HPLC marker profile, was used as the batch-release specification against which the toxicological findings below are interpreted — that is, all toxicology data reported here pertain specifically to a batch meeting this defined composition, not to rosemary extract in general.

## Acute Oral Toxicity Findings

No mortality occurred in any animal at the 2000 mg/kg limit dose over the 14-day observation period. Transient, mild sedation and reduced spontaneous activity were noted in 3/5 treated animals within the first 2 hours post-dosing, resolving fully by 6 hours; no other clinical signs were recorded. Mean body weight gain in treated animals (32.6 ± 4.1 g over 14 days) did not differ significantly from control (34.8 ± 3.6 g, $p=0.31$). Terminal necropsy revealed no macroscopic organ abnormalities, and relative liver, kidney and spleen weights in treated animals were within 5% of control values with no statistically significant differences. On this basis the extract was classified as Category 5 (or unclassified) under the Globally Harmonized System, with an oral LD50 estimated to exceed 2000 mg/kg, and a no-observed-adverse-effect level (NOAEL) for this single-dose protocol set at the limit dose of 2000 mg/kg — consistent with the absence of mortality reported by Anadón et al. at comparable dose levels for a different rosemary extract preparation [13].

## In Vitro Cytotoxicity Screening Results

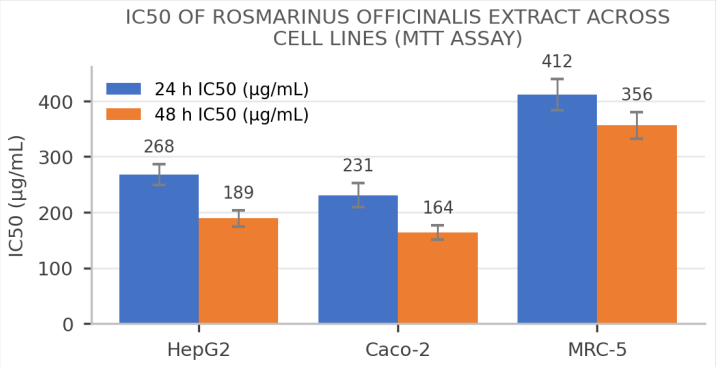
Concentration-dependent reductions in cell viability were observed in all three lines, but with a clear separation between the normal fibroblast line and the two lines with faster baseline proliferation rates (Table 2). At 24 hours, IC50 values were 412 ± 28 µg/mL in MRC-5, 268 ± 19 µg/mL in HepG2, and 231 ± 22

µg/mL in Caco-2; by 48 hours these fell to 356 ± 24, 189 ± 15, and 164 ± 13 µg/mL respectively, reflecting a modest time-dependent component to the cytotoxic effect. No line showed meaningful loss of viability below 50 µg/mL at either timepoint, which we take as the more pharmaceutically relevant threshold given the extract concentrations likely to be relevant in a finished oral dosage form after dilution and metabolism.

***HPLC marker-compound content and GC-MS volatile profile of the freeze-dried Rosmarinus officinalis ethanolic extract (mean ± SD, n=3 batches).***

| Constituent | Method | Content | Unit |
|---|---|---|---|
| Rosmarinic acid | HPLC-DAD (330 nm) | 6.82 ± 0.31 | % w/w |
| Carnosic acid | HPLC-DAD (230 nm) | 4.15 ± 0.24 | % w/w |
| Carnosol | HPLC-DAD (230 nm) | 1.38 ± 0.09 | % w/w |
| Total phenolic content | Folin-Ciocalteu | 142.6 ± 5.8 | mg GAE/g extract |
| 1,8-Cineole | GC-MS (% TIC) | 21.4 | % of TIC |
| Camphor | GC-MS (% TIC) | 14.7 | % of TIC |
| α-Pinene | GC-MS (% TIC) | 9.2 | % of TIC |
| Verbenone | GC-MS (% TIC) | 5.6 | % of TIC |
| Borneol | GC-MS (% TIC) | 3.9 | % of TIC |
| β-Caryophyllene | GC-MS (% TIC) | 2.4 | % of TIC |

***In vitro cytotoxicity (24 h and 48 h IC50, MTT assay) of the Rosmarinus officinalis ethanolic extract in HepG2, Caco-2 and MRC-5 cell lines. Error bars show SD of three independent experiments.***




## Genotoxicity Battery Outcomes

The Ames assay was negative across all five tester strains, with and without S9 activation, at every concentration tested up to and including the maximum recommended concentration (5000 µg/plate); revertant colony counts in extract-treated plates did not exceed twice the concurrent solvent-control mean at any concentration, and positive controls (sodium azide, 2-aminoanthracene, 4-nitroquinoline-1-oxide as appropriate to strain/activation condition) performed as expected. The in vitro micronucleus assay likewise returned a negative result: binucleated-cell micronucleus frequency in extract-treated lymphocyte cultures ranged from 0.42% to 0.58% across the tested concentration range (both treatment regimens), statistically indistinguishable from the vehicle-control frequency of 0.39% (p=0.62) and well below the frequency induced by the mitomycin C positive control (4.1%). No dose-related cytotoxicity sufficient to trigger the guideline's dose-selection ceiling was observed below 600 µg/mL. The comet assay in HepG2 cells showed a small increase in mean tail intensity at the two highest concentrations tested (400 and 800 µg/mL: 8.9 ± 1.6% and 11.2 ± 2.1% DNA in tail, respectively, versus 6.1 ± 1.3% in vehicle control), but this increase tracked closely with the concentration-dependent cytotoxicity already characterised in the MTT screen at those same concentrations, and did not meet the pre-specified criteria for a genotoxic (as opposed to cytotoxicity-associated) positive call.

***Summary of the acute oral toxicity and genotoxicity battery findings for the Rosmarinus officinalis ethanolic extract.***

| Assay | Guideline | Test system | Result |
|---|---|---|---|
| Acute oral toxicity (limit test) | OECD 423 | Sprague-Dawley rats, 2000 mg/kg single dose | No mortality; NOAEL = 2000 mg/kg (limit dose) |
| Bacterial reverse mutation (Ames) | OECD 471 | S. typhimurium TA98/TA100/TA1535/TA1537, E. coli WP2 uvrA, ±S9 | Negative, all strains, up to 5000 µg/plate |
| In vitro micronucleus | OECD 487 | Human peripheral blood lymphocytes, ±S9 | Negative; 0.42–0.58% vs 0.39% control (p=0.62) |
| Alkaline comet assay | Tice et al. 2000 guidelines | HepG2 cells | No genotoxic call; tail-intensity increase tracked with cytotoxicity only |

## Discussion

Two things stand out when the phytochemical and toxicological halves of this dataset are read together rather than separately. First, the extract characterised here sits comfortably within the compositional range reported previously for ethanolic rosemary preparations — rosmarinic acid in the mid-single-digit percentage range, carnosic acid somewhat lower, and carnosol lower still, reflecting partial but not extensive oxidative conversion [3,17]. That places this batch closer to the "fresh, well-stored extract" end of the spectrum described by Zhang and colleagues rather than an aged or heat-stressed preparation in which carnosol and downstream degradation products would dominate [2]. Because carnosic acid itself is reported to carry much of the pro-apoptotic and antiproliferative activity attributed to rosemary extract in cancer cell line studies [8,4], a batch with this ratio would be expected to show somewhat more pronounced in vitro cytotoxic potency than a degraded, carnosol-dominant extract — and indeed the IC50 values obtained here (160-400 µg/mL depending on cell line and timepoint) sit toward the more potent end of ranges reported elsewhere for rosemary extract cytotoxicity screens, without crossing into concentrations that would raise a red flag for a topical or oral nutraceutical application at realistic use concentrations.

Second, the absence of a genotoxic signal here — negative Ames, negative micronucleus, and a comet-assay response that tracks cytotoxicity rather than true DNA-reactive damage — replicates what has already been reported for differently prepared rosemary extracts in dedicated regulatory toxicology studies [15]. That consistency across extraction methods (this study's ethanolic

extract versus the supercritical CO2 and acetone extracts examined by Phipps et al.) is reassuring precisely because genotoxicity is one of the endpoints where extract-to-extract compositional variability might plausibly matter: if a genotoxic signal were being driven by a minor, solvent-dependent contaminant rather than by the core rosmarinic acid/carnosic acid/carnosol chemistry, one would expect divergent results between extraction methods rather than convergent negative findings. The acute oral toxicity result — no mortality and no clinically important findings at the 2000 mg/kg limit dose — likewise sits comfortably alongside the acute study reported by Anadón et al. using a supercritical-fluid rosemary extract [13] and the broader safety picture summarised in the recent comprehensive review of rosemary toxicology [16], as well as with EFSA's repeated conclusions, across three separate opinions spanning food, exposure-refinement, and companion-animal feed contexts, that rosemary extract carries a wide margin of safety at realistic exposure levels [1,10,11].

None of this should be read as a blanket "rosemary extract is safe, full stop" conclusion, and we want to resist that temptation because it is exactly the oversimplification that a compositional case study like this one is meant to push back against. The reproductive/developmental toxicity screening data available in the literature relate to acetone extracts rather than the ethanolic extract characterised here [14], and while there is no obvious chemical reason to expect a materially different reproductive toxicity profile given the overlapping marker-compound chemistry, that is an inference rather than a directly tested claim, and a formulation programme intending chronic or reproductive-age dosing would still need extract-specific reproductive toxicity data rather than relying on read-across from a different solvent system. Likewise, the mild sedative signs observed transiently in the acute toxicity arm are a reminder that even "safe" botanical extracts are not pharmacologically inert — 1,8-cineole and camphor, both present at meaningful concentrations in the volatile fraction characterised by GC-MS here, have their own CNS activity profiles at sufficient exposure, and a pharmaceutical development programme would want to track these constituents as potential drivers of tolerability findings rather than treating "extract dose" as a single undifferentiated variable.

From a pharmaceutical development standpoint, the practical implication of pairing phytochemical fingerprinting with toxicology data this tightly is that batch specification becomes part of the safety case, not just a quality-control afterthought. A finished product claim built on "rosemary extract standardised to X% carnosic acid, Y% rosmarinic acid, with this GC-MS volatile signature" is a claim that can be defended against a specific toxicology dataset generated on material meeting that same specification — which is a meaningfully stronger regulatory position than citing generic literature on "rosemary extract" as a category. Given the cytotoxicity margins observed here relative to the doses that would realistically be delivered in an oral nutraceutical capsule or a topical antioxidant formulation, and given the negative genotoxicity battery and the favourable acute oral toxicity outcome, this particular extract lot looks like a reasonable candidate to carry forward into formulation development, with the caveat that a repeated-dose (28- or 90-day) study on this same batch would be the logical next step before any chronic-use product claim is made.

## Conclusion

This case study characterised a single, well-defined ethanolic *Rosmarinus officinalis* extract batch by HPLC (rosmarinic acid 6.82%, carnosic acid 4.15%, carnosol 1.38% w/w) and GC-MS (1,8-cineole, camphor and α-pinene as the dominant volatiles), and ran that same batch through an acute oral toxicity limit test, a three-cell-line cytotoxicity screen, and a full genotoxicity battery. No mortality or genotoxic signal was observed, and cytotoxic potency (IC50 160-410 µg/mL depending on cell line and exposure time) sat within a range that leaves a comfortable margin against realistic pharmaceutical or nutraceutical use concentrations. These findings are consistent with, and add batch-specific detail to, the existing regulatory and toxicological literature on rosemary extract safety. We would flag repeated-dose and, if chronic dosing is intended, reproductive toxicity testing on this specific extract specification as the natural next steps before formulation work proceeds to later-stage development.

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