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Chronopharmacology of Herbal Extracts: Influence of Administration Timing on Pharmacokinetic and Pharmacodynamic Responses — A Narrative Review

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Abstract

Background: Circadian rhythms influence physiological processes involved in absorption, metabolism and biological responses to pharmacologically active compounds. Although chronopharmacology is well established as a general principle, the importance of administration timing for herbal preparations remains insufficiently characterized. Objective: To critically examine published experimental evidence on time-of-day effects on the pharmacokinetic and pharmacodynamic responses to herbal extracts. Approach: This narrative synthesis considers directly comparative preclinical studies of botanical preparations administered at different circadian phases, together with selected mechanistic literature. Findings: Rat investigations with grape seed proanthocyanidin extract have identified administration-time-dependent differences in plasma phenolic metabolites, serum metabolomic responses and hepatic lipid-related outcomes. These responses may also vary with sex and dietary context. An earlier rat investigation involving a Ginkgo biloba preparation reported schedule- and time-related differences in psychotropic responses. Circadian variation in gastrointestinal physiology, metabolism, tissue clocks and microbial biotransformation offers plausible explanatory pathways, but these mechanisms cannot be assumed to account for every extract-specific effect. Conclusion: Administration timing is a promising experimental variable in botanical pharmacology, but current evidence is predominantly preclinical and concentrated in relatively few extracts. Standardized phase reporting, rigorous extract characterization and clinically relevant outcomes are required before optimal dosing-time recommendations can be established.

Keywords: Chronopharmacology; Herbal extracts; Circadian rhythm; Chronopharmacokinetics; Phytotherapy.

1. Introduction

Herbal extracts are chemically complex preparations whose constituent concentrations and biological effects depend on plant material, extraction procedures, formulation and the recipient's physiology. A frequently overlooked determinant is the time at which an extract is administered. Endogenous circadian oscillations organize metabolism, endocrine signalling, sleep–wake behaviour and cellular responses across approximately 24 hours. Consequently, identical doses delivered at different biological phases need not produce identical exposure or effects [1,2].

Chronopharmacology concerns time-dependent variation in drug action. Chronopharmacokinetics focuses on absorption, distribution, metabolism and elimination, whereas chronopharmacodynamics addresses variation in target sensitivity and downstream biological responses. These concepts should not be conflated with studies in which phytochemicals themselves alter circadian clocks: an extract may modulate a rhythm without its therapeutic effect having been compared across administration times.

This review examines what has actually been demonstrated for botanical extracts, identifies plausible mechanisms and discusses how experimental design can move the field toward interpretable and reproducible results. It does not presume that morning administration is preferable to evening administration.

2. Review approach and scope

This article is a narrative, not systematic, review. The initial evidence set was assembled from identifiable PubMed and publisher records for experimental studies involving "administration

time", "grape seed proanthocyanidin extract", "Ginkgo biloba", "circadian", and "chronopharmacology", alongside relevant mechanistic articles. Studies were discussed as direct timing comparisons only when distinct dosing phases were reported. Circadian-modulation studies without a between-time dosing comparison were considered supportive rather than proof of optimal timing. No exhaustive database screening, preregistered protocol, risk-of-bias scoring or quantitative meta-analysis was performed; therefore, absence of evidence in this paper must not be interpreted as proof that no other studies exist.

3. Biological rationale for time-dependent responses

3.1 Central and peripheral clocks

Mammalian circadian organization involves the suprachiasmatic nucleus and peripheral oscillators in organs including liver and intestine. Molecular feedback loops involving CLOCK/BMAL1 and PER/CRY coordinate rhythmic gene expression. External light synchronizes the central pacemaker, whereas food availability and other cues may influence peripheral phase. Thus, clock time alone is an inadequate descriptor of biological phase across species or laboratory conditions [1,2].

3.2 Pharmacokinetic pathways

Gastric motility, intestinal transport, hepatic metabolic activity and renal handling may fluctuate across the day. For plant polyphenols, measured plasma exposure additionally reflects conjugation reactions and conversion by intestinal microbiota. These processes make a plausible case for time-sensitive systemic availability; nevertheless, a mechanistic possibility should not be presented as demonstrated clinical benefit. The grape seed experiment described below offers direct evidence of timing-dependent phenolic metabolite profiles [3].

3.3 Pharmacodynamic pathways

Time-varying tissue responsiveness may change the magnitude of behavioural, inflammatory or metabolic outcomes at a given exposure. A change in pharmacodynamic effect need not arise from a change in absorption, and a change in metabolite concentration need not establish improved efficacy. Ideally, studies should measure both exposure and prespecified functional endpoints to distinguish these explanations.

4. Direct experimental evidence

4.1 Grape seed proanthocyanidins: bioavailability

Escobar-Martínez and colleagues administered grape seed proanthocyanidin extract (GSPE; 25 mg/kg/day) to male and female Fischer 344 rats at 08:00 (ZT0) or 20:00 (ZT12) during the last four weeks of a nine-week dietary protocol [3]. Rats received standard or cafeteria diets. Liquid chromatography–tandem mass spectrometry was used to characterize circulating phenolic metabolites. Administration time affected several phase-II and microbiota-derived phenolic metabolites, with additional influences of diet and sex. The study directly supports a chronopharmacokinetic effect, but metabolite differences should not automatically be equated with a superior therapeutic outcome.

4.2 Grape seed proanthocyanidins: systemic metabolome

Arreaza-Gil and colleagues investigated GSPE at ZT0 and ZT12 in female and male Fischer 344 rats exposed to standard or cafeteria diets [4]. Their findings indicated time-dependent variation in serum amino-acid, lipid and cholate-related metabolites, associated with measures of central clock-gene expression. Sex and diet modified the responses. The results extend the question beyond exposure to downstream metabolic profiles, but metabolomics is primarily hypothesis-generating: altered metabolite patterns do not independently establish clinical benefit.

4.3 Grape seed proanthocyanidins: hepatic outcomes

Rodríguez and colleagues reported that GSPE affected diurnal patterns of hepatic metabolic genes and metabolites in cafeteria-fed rats, with a time-of-day-dependent reduction in hepatic lipid deposition [5]. This provides stronger functional relevance than exposure data alone.

However, the specific dietary model and rodent circadian phase constrain translation to human metabolic disease. It also remains important to separate effects of administration phase from potential effects of sampling phase.

4.4 Ginkgo biloba and adaptogenic preparations

Arushanian and Naumov compared psychotropic and chronotropic properties of plant-origin preparations, including a Ginkgo biloba extract marketed as Bilobil, and melatonin in rats [6]. The PubMed abstract reports effects on memory, locomotion, exploratory behaviour and anxiety, with different chronotropic properties depending on acute versus repeated dosing and morning versus evening administration. The article is in Russian and only its English abstract was used here; consequently, the direction and size of extract-specific comparisons cannot be verified from the available abstract. This study is a signal for further investigation, not a basis for recommending a particular Ginkgo dosing time.

5. Summary of direct studies

Study	Model / comparison	Principal outcome	Interpretive caution
Escobar-Martínez et al., 2022 [3]	Fischer 344 rats; GSPE at ZT0 vs ZT12	Phenolic metabolite bioavailability differed	Exposure is not efficacy
Arreaza-Gil et al., 2023 [4]	Male/female rats; diet groups; ZT0 vs ZT12	Serum metabolome and clock-associated responses varied	Sex and diet modified findings
Rodríguez et al., 2024 [5]	Cafeteria-fed rats; dosing-phase comparison	Hepatic rhythms and lipid deposition affected	Model-specific functional outcome
Arushanian & Naumov, 2010 [6]	Rats; Ginkgo-containing comparison; morning vs evening	Time- and schedule-related behavioural effects	Abstract-level evidence only

6. Interpretation of the evidence

The most persuasive conclusion is narrow: administration phase can alter selected pharmacokinetic and metabolic responses to at least some botanical extracts in controlled animal models. GSPE has been studied using direct ZT0/ZT12 contrasts across multiple outcome domains [3–5]. These papers also show why a simple "morning is better" conclusion would be unsound: the endpoint, sex, diet and biological phase all matter.

The evidence base is not evenly distributed across botanicals. Several of the most informative reports concern GSPE and overlapping scientific groups; multiple publications should not be mistaken for broad independent replication across unrelated herbs. Ginkgo data provide an interesting precedent, but extract standardization, access to detailed methods and replication remain important limitations [6].

For nocturnal rodents, ZT0 generally corresponds to light onset and the beginning of their usual resting phase, whereas ZT12 corresponds to dark onset and their usual active phase. Human diurnal activity patterns differ. Therefore, directly translating "morning" and "evening" labels from rat studies into human dosing recommendations risks reversing the relevant biological context.

7. Methodological priorities for future research

Future investigations should prespecify whether the primary hypothesis concerns exposure, efficacy or safety; report the light–dark schedule and Zeitgeber time; characterize the botanical extract and its marker constituents; and control feeding and handling schedules. Studies should also assess sex as a biological variable, use consistent sampling intervals after dosing, and consider whether observed changes are driven by pharmacokinetics or pharmacodynamics.

Repeated dosing may entrain or modify biological rhythms and should be distinguished from acute administration. To isolate timing effects, groups should receive the same extract dose, vehicle and duration, with handling controls at both phases. Where feasible, investigators should measure plasma or tissue concentrations alongside functional endpoints and include a suitable circadian sampling series rather than a single terminal time point.

Aquatic experimental systems, including zebrafish, may provide opportunities to explore time-of-day effects on behaviour and neurobiological endpoints. However, waterborne exposure introduces additional variables such as compound stability, uptake kinetics and photoperiod-dependent activity. Any proposed zebrafish dosing schedule should be justified with species-specific circadian physiology rather than extrapolated directly from rat studies.

8. Research gaps and clinical translation

A central gap is the scarcity of adequately replicated, directly comparative studies across different standardized herbal preparations. Extract composition can differ markedly even when botanical species are the same. Many experiments prioritize biochemical or omics readouts without clinically meaningful efficacy endpoints. Furthermore, the extent to which timing effects persist in patients with disrupted sleep, shift work, comorbidities or polypharmacy remains uncertain.

Clinical trials would need to compare clearly defined administration phases under realistic dosing conditions and account for chronotype, meals and concomitant medicines. Until such studies are available, routine recommendations to administer particular herbal extracts in the morning or evening should not be inferred from rodent metabolomic results alone.

9. Conclusion

Administration timing is an experimentally supported determinant of some responses to herbal extracts, with the clearest directly comparative evidence in this review coming from grape seed proanthocyanidin preparations. The available literature also illustrates considerable dependence on the measured outcome and biological context. The next step is not to declare an optimal universal dosing time, but to conduct standardized, mechanistically informed experiments and translational studies that determine when timing produces a meaningful difference in efficacy or safety.

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