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A Systematic Review of Bioactive Metabolites and Antioxidant Potential of *Sawo Duren (Chrysophyllum spp.)*: Integrating Evidence from Metabolomic and Chemometric Studies

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Abstract: Chrysophyllum spp. contains diverse bioactive metabolites, including polyphenols, flavonoids, and triterpenes such as lupeol, which contribute to their antioxidant, antiparasitic, and cytotoxic activities. However, most existing studies rely on basic phytochemical analyses and have not incorporated metabolomic or chemometric approaches capable of providing comprehensive metabolite profiling. This systematic review synthesizes current evidence on the bioactive metabolites and antioxidant potential of *Chrysophyllum* spp. and evaluates the extent to which advanced analytical techniques have been applied. The included studies report high levels of polyphenols and triterpenes, with notable antioxidant effects mediated through enhanced SOD, CAT, and GPx activities and reduced oxidative stress. Polyphenolic compounds also exhibit cytotoxicity via ROS induction in cancer cells, while lupeol and its derivatives demonstrate promising antiparasitic activity. Despite these findings, the lack of high-resolution metabolomics and chemometric integration limits the identification of key metabolites and mechanistic understanding. Overall, *Chrysophyllum* spp. represent a potential natural source of biologically active metabolites, particularly antioxidants. Future research using advanced metabolomic and the chemometric methodologies is essential to achieve comprehensive metabolite mapping and clarify the mechanisms underlying their bioactivities.

Keywords: Antioxidants; Chemometrics; *Chrysophyllum spp.*; Flavonoids; Lupeol

Introduction

Research on bioactive metabolites and antioxidant potential in tropical plants has expanded rapidly in response to the growing demand for natural antioxidants that are safer and more effective than their synthetic counterparts, particularly in preventing oxidative damage associated with various degenerative diseases (Mendonça et al., 2022; Rudrapal et al., 2022; Tumilaar et al., 2024). The sawo duren plant (*Chrysophyllum* spp.), a member of tropical flora, holds substantial pharmaceutical potential due to its rich content of secondary metabolites such as flavonoids, phenolics, and triterpenoids (Agiel et al., 2024), all of which have been reported to exhibit important biological activities. Comprehensive studies examining the health benefits of this plant have identified several bioactive compounds including quercetin, catechin, gallic acid, procyanidins, β-amyrin, and lupeol, each contributing to antioxidant, antidiabetic, anti-inflammatory, and antiproliferative effects (Jain et al., 2025; Ritika et al., 2024). Moreover, recent investigations have demonstrated notable variations in metabolite composition among the leaves, fruits, and seeds, which account for the differences in antioxidant activity across plant parts. These findings underscore the relevance of employing high-resolution metabolomic approaches to further elucidate the chemical diversity of *Chrysophyllum* spp. (Lawal et al., 2010). Metabolomics is particularly essential because conventional phytochemical methods

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are insufficient for capturing a comprehensive and in-depth metabolite profile (Bansal et al., 2025; Goel et al., 2026; Munjal et al., 2022). In addition, previous studies have indicated that metabolites in *Chrysophyllum* spp. confer biological protection against oxidative stress at both cellular and tissue levels, further supporting the scientific relevance of continued exploration of this plant (Sultana et al., 2023). Therefore, a systematic review of the bioactive metabolites and biological activities of sawo duren is urgently needed to provide a more comprehensive, standardized, and scientifically grounded understanding of its pharmacological potential.

The urgency of this research is further strengthened by empirical evidence demonstrating that the active metabolites of *Chrysophyllum* spp. can substantially reduce oxidative damage. An in vivo study reported that leaf extracts of this plant significantly increased the activities of antioxidant enzymes such as SOD, CAT, and GPx while decreasing malondialdehyde (MDA) levels in gamma-irradiated rats, indicating a strong protective effect against severe oxidative stress. In parallel, findings by (Li et al., 2015) revealed that polyphenolic fractions of *Chrysophyllum* spp. fruit not only exhibited antioxidant activity in vitro but were also capable of elevating ROS levels in osteosarcoma cells, thereby inducing apoptosis. This dual behavior highlights that the plant's metabolites function as antioxidants under normal physiological conditions while simultaneously exerting selective pro-oxidant effects beneficial for cancer therapy. Further supporting its pharmacological relevance, studies examining the antiparasitic potential of lupeol acetate, one of the major metabolites in *Chrysophyllum* spp., confirmed the importance of this compound, particularly after structural modifications were shown to markedly enhance antiparasitic efficacy and synergize with metronidazole (Adebayo et al., 2011). Collectively, these findings underscore that the plant's bioactive metabolites not only act as antioxidants but also possess a broader spectrum of biological activities, reinforcing their potential for natural product-based drug development (Chintada & Golla, 2025). Therefore, consolidating the available scientific evidence through a systematic approach is essential to generate stronger and more integrated conclusions regarding the therapeutic value of *Chrysophyllum* spp. (Kumar Padarthi et al., 2024; Najmi et al., 2022).

Despite its promising potential, most previous studies have employed limited and non-comprehensive analytical approaches. Many investigations have relied solely on basic antioxidant assays such as DPPH, FRAP, or ABTS without conducting in-depth metabolite identification using metabolomic techniques such as LC-MS or LC-HRMS, resulting in incomplete information on the metabolite profiles that contribute to the observed biological activities (Edlund *et al*., 2022). In addition, studies evaluating metabolite variations across different plant parts remain restricted to simple parameters such as total phenolic content (TPC) and total flavonoid content (TFC), which are inadequate for elucidating the complex interactions among metabolites that may influence antioxidant potential. Notably, the findings of (Zhu et al., 2026) suggest that phenolic and flavonoid compounds do not act in isolation but rather operate through integrated mechanisms that modulate multiple biological pathways. Moreover, a review by (Doan, 2020) emphasized that *Chrysophyllum* spp. contain numerous metabolites that remain insufficiently explored, highlighting a significant knowledge gap in understanding metabolite–activity relationships comprehensively. Therefore, the application of metabolomic and chemometric methods in this research is expected to provide broader and more accurate insights into the metabolite spectrum and its association with the biological activities of *Chrysophyllum* spp. Based on this background, the present study aims to conduct a Systematic Literature Review (SLR) on the bioactive metabolites and antioxidant potential of sawo duren (*Chrysophyllum* spp.) by integrating evidence from available metabolomic and chemometric studies. The objectives of this research are to identify, classify, and evaluate the existing evidence on metabolite profiles, antioxidant activity, and the relationships between specific metabolites and their associated biological properties. In addition, this study seeks to identify research gaps, elucidate patterns of metabolite distribution across different plant parts, and propose future research directions that are more targeted and scientifically grounded.

The relevance of this study to the existing literature is well-established, as all included articles are rooted in biochemical, phytochemical, and bioactivity research on *Chrysophyllum* spp., which has been scientifically recognized for its therapeutic potential. Through the integration of these findings in a structured SLR, this study is expected to provide a holistic overview of the strengths and limitations of current evidence and to clarify the scientific position of *Chrysophyllum* spp. within the broader context of natural product development as a promising source of natural antioxidants. The research questions of this study can be formulated as follows. First, what are the profiles of bioactive metabolites that have been identified in sawo duren (*Chrysophyllum* spp.) based on previous research? Second, what is the antioxidant potential of this plant according to scientific evidence derived from various plant parts, including the leaves, fruits, stems, and seeds? Third, how do specific metabolites relate to antioxidant activity as reported through metabolomic and chemometric analyses? Fourth, what research gaps remain in the existing literature concerning the metabolites and biological activities of this plant? Finally, how can the findings of this SLR be utilized as a foundation for future studies, particularly in the development of natural antioxidant products? By addressing these research questions, this study is expected to provide a significant scientific contribution by enhancing the understanding of the pharmacological potential of *Chrysophyllum* spp. and supporting the development of phytopharmaceuticals derived from tropical biological resources.

Method

This study employed a descriptive research design using a Systematic Literature Review (SLR) approach. A comprehensive literature search was conducted using the Watase UAKE application on the Scopus database with the keyword "*Chrysophyllum cainito*." The article selection process followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

The primary objective was to identify, extract, and synthesize primary evidence regarding the metabolite profiles and antioxidant potential of *Chrysophyllum* spp. through a transparent analytical framework (Doan, 2020). The "sample" characteristics in this SLR consisted of primary studies reporting phytochemical data, antioxidant assays (e.g., DPPH), in vitro or in vivo outcomes (e.g., antioxidant enzyme assays, MDA levels), or metabolite profiling/chemometric analyses (e.g., LC profiling, LC-HRMS when available). Review articles without primary data were excluded (Li et al., 2015). Data extraction was performed using a structured extraction form that included study identification, sample type (leaf, fruit, stem, seed), preparation methods, analytical conditions (chromatographic/spectrometric techniques), antioxidant parameters (IC_{50} values, TPC in mg GAE/g), and the list of identified metabolites along with spectrometric evidence when reported (Doan, 2020). The data collection process consisted of several steps: formulation of research questions, establishment of inclusion and exclusion criteria, screening of titles and abstracts, full-text assessment, structured data extraction, and cross-verification by at least two reviewers to minimize extraction bias. Any discrepancies were resolved through discussion and reference to the original text (Mokari et al., 2023). For studies reporting metabolomic data, additional extraction steps included documentation of ionization methods, m/z ranges, deconvolution/peak-picking processes, and identification strategies (library matching or reference standards) to ensure detailed metabolite identification (Requena et al., 2019).

Data analysis techniques included methodological quality assessment, harmonization of numerical data units, metabolomic data normalization (e.g., normalization to total ion current or sample weight), and narrative–quantitative synthesis. When feasible, reproducible chemometric analyses such as PCA were applied to explore variability, while PLS-DA was used to identify important features (VIP) associated with antioxidant activity (Doan, 2020). All documentation steps, including reasons for exclusion and extraction forms, were recorded to ensure reproducibility, enabling other researchers to replicate the protocol without ambiguity (Zhu *et al.*, 2026).

Result and Discussion

The results of the article search from the Scopus database are presented in the diagram below (Figure 1).

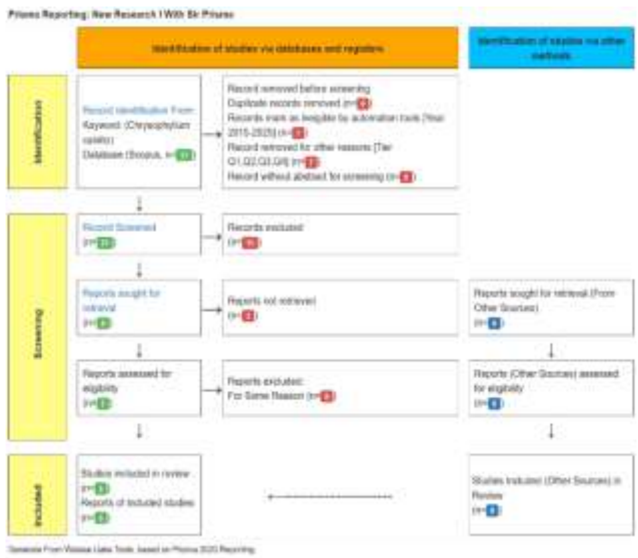

Figure 1. PRISMA diagram

Based on the PRISMA diagram presented in Figure 1, the initial identification process yielded 37 records from the Scopus database using the keyword *Chrysophyllum cainito*. Fourteen records were removed prior to screening because they did not meet the preliminary criteria (seven records were outside the publication range of 2015–2025 and seven records were published in journals outside the Q1–Q4 tiers), leaving 23 records for title and abstract screening. At this stage, 15 records were excluded due to irrelevance to the research focus, and only 8 records proceeded to full-text assessment. During the full-text evaluation, 5 reports were successfully retrieved, while 3 reports were not accessed. Subsequently, all five accessible studies were assessed for eligibility, and all met the inclusion criteria without any exclusions. Therefore, the final number of studies included in the Systematic Literature Review was 5, all of which were considered relevant and suitable for further analysis. This diagram illustrates a rigorous, transparent, and systematic selection process in accordance with the PRISMA 2020 standards.

The results of the article search based on the keyword query in the database are presented in the figure below (Figure 2).

Figure 2. Word Cloud Visualization

Based on the word cloud visualization in Figure 2, it is evident that research on *Chrysophyllum cainito* L., commonly known as star apple or caimito, is strongly centered on the phytochemical and bioactivity aspects of this species. Keywords such as *Sapotaceae*, polyphenols, triterpenes, gallic acid, and lupeol acetate emphasize that this plant is rich in important secondary metabolites with broad pharmacological potential. The prominent appearance of terms such as *antioxidant*, *antioxidant activity*, and *oxidative stress* indicates that antioxidant activity is a dominant theme in *C. cainito* research, consistent with the well-established ability of polyphenols and triterpenes to neutralize free radicals. The presence of terms such as *antisteoporosis*, *macrophages*, and *hypersensitivity* suggests that the plant's bioactivity extends beyond antioxidant mechanisms and includes modulation of immune responses and potential therapeutic effects on bone tissue. Additionally, the inclusion of terms like *molecular docking* and *domestication* reflects the adoption of modern analytical approaches in bioactivity studies as well as the growing research interest in the conservation and domestication of this species. Overall, the word cloud indicates that *Chrysophyllum cainito* is a research-rich species with significant biological, phytochemical, and therapeutic value, with particular emphasis on its metabolites as promising antioxidant agents and bioactive molecules.

The results of the keyword-based search by publication year in the database are presented in the figure below (Figure 3).

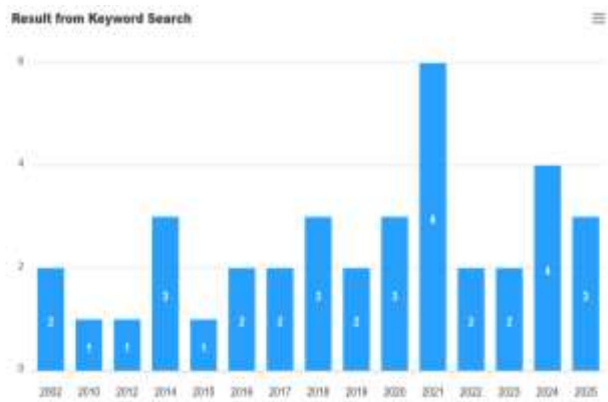

Figure 3. Keywords by Year

Based on the annual keyword search results presented in Figure 3, the analysis of publication trends shows fluctuations in research intensity from 2002 to 2025. In the early phase (2002–2012), the number of publications remained low and sporadic, reflecting limited scientific attention to this topic. Beginning in 2014, the trend started to rise with several minor peaks, followed by a relatively stable period between 2017 and 2020 with two to three publications per year. The highest peak occurred in 2021, with six publications, indicating a significant surge in academic interest. After a temporary decline in 2022–2023, the graph shows an increase again in 2024 and stabilization in 2025. Overall, this trend suggests a gradual growth in research activity, accompanied by dynamic shifts in scientific interest influenced by methodological developments and thematic relevance.

Article Search Profile

The article search profile (Table 1), based on the specified keywords, demonstrates a fluctuating pattern of publications from 2002 to 2025, reflecting shifts in the level of scientific attention devoted to the topic. In the early years, the number of publications was limited, indicating an initial exploratory phase in the scientific investigation of this subject. Beginning in 2014, research interest began to rise, marked by several notable peaks and a period of consistent growth between 2017 and 2020. The highest peak occurred in 2021, reflecting a significant surge in scholarly interest, possibly influenced by methodological advancements or newly emerging findings. Following a decline in 2022–2023, the number of publications increased again in 2024 and remained stable in 2025. Overall, this profile indicates that research on the topic has experienced gradual growth with varying intensities, suggesting a continuously expanding scientific interest over the past two decades.

Table 1. The articles profile result

Authors (Year)	Country	Journal and Impact Factor	Study Design	Research Object
(Sayed et al., 2019)	Egypt	*Biomedicine & Pharmacotherapy* (IF 1.62)	In vivo experimental study using rats and leaf extract	Gamma-irradiated rats; *C. cainito* leaves
(Doan, 2020)	Vietnam	*Evidence-Based Complementary and Alternative Medicine* (IF 0.86)	Narrative literature review	Various parts of *C. cainito* and active compounds
(Li et al., 2015)	China	*Bangladesh Journal of Pharmacology* (IF 0.28)	In vitro cytotoxicity assay of polyphenolic fruit fractions	Osteosarcoma cells; polyphenolic fruit fraction
(Herrera-españa et al., 2022)	Mexico	*Natural Product Research* (IF 0.37)	Chemical synthesis and in vitro antiparasitic assay	Lupeol acetate derivatives from *C. cainito* fruit
(Figueiredo et al., 2023)	Brazil	*Anais da Academia Brasileira de Ciências* (IF 0.33)	Phytochemical characterization and antioxidant assays (leaf, fruit, seed)	Leaves, fruits, and seeds of *C. cainito*

Among the articles obtained in this review, several were published in journals with reported impact factors. The impact factor represents the average number of citations received by articles published in a journal and is commonly used to indicate the journal's scholarly influence within a specific time frame. However, the impact factor does not directly reflect the quality of an individual article; rather, it serves only as an indicator of the journal's ranking during a given publication period.

Previous studies have demonstrated that *Chrysophyllum cainito* is a significant source of bioactive metabolites, particularly polyphenols, flavonoids, and triterpenes such as lupeol, which contribute to its antioxidant, cytotoxic, and antiparasitic activities. The in vivo study conducted provides strong experimental evidence of the antioxidant activity of *C. cainito* leaf extract, as indicated by increased activities of endogenous enzymes such as SOD, CAT, and GPx, along with improvements in hematological profiles and hepatic and renal histology in gamma-irradiated rats. These protective effects are attributed to the presence of polyphenols and flavonoids that function as free radical scavengers. However, the study presents several methodological limitations, including the absence of HRMS-based metabolite identification, the use of a single dosage, and the lack of in vitro validation in specific cellular models.

Meanwhile, the study conducted by Herrera-españa et al. (2022)highlights the bioactive potential of lupeol acetate, a key triterpenoid in *C. cainito*, through the synthesis of N-alkyl-arylsulfonamide derivatives and in vitro evaluation of their antiparasitic activity. The findings demonstrate that structural modification of lupeol can enhance its antiparasitic potency and produce synergistic interactions with metronidazole. Nevertheless, this study did not assess antioxidant activity nor incorporate metabolomic exploration, leaving an open research space regarding the contribution of this triterpenoid to the broader metabolite profile of *Chrysophyllum* spp. Furthermore, the comprehensive narrative review by Doan (2020) identified several major active metabolites in *C. cainito*, including quercetin, catechin, gallic acid, procyanidins, lupeol, and β-amyrin, along with their associated biological activities particularly antioxidant mechanisms mediated by polyphenols and flavonoids (de Carvalho et al., 2020). Although the review provides an extensive overview of the plant's bioactivity profile, its primary limitation lies in the predominance of in vitro studies, resulting in insufficient clinical evidence.

The recent phytochemical study published in (Ogbu et al., 2024) provides additional insights through the characterization of metabolites in different plant parts—leaves, fruits, and seeds using TPC/TFC measurements, liquid chromatography profiling, and antioxidant assays including DPPH, ABTS, and FRAP. The study revealed significant variations in phenolic and flavonoid composition among the plant parts, which directly influence their antioxidant capacity.

Table 2. Relevant articles from exploration results

Research titles	Author	Key Insights	Theory Used	Method	Result	Limitations	Correlation with Research
Modulatory effects of Chrysophyllum cainito	(Ogbu et al., 2024)	C. cainito leaf extract is able to reduce oxidative	Radiation increases ROS → cell damage; polyphenols/flavon	Methanolic extraction of leaves, phytochemic	Increased antioxidant enzymes, decreased	No metabolite identification via HRMS,	Supporting that the active metabolites

Research titles	Author	Key Insights	Theory Used	Method	Result	Limitations	Correlation with Research
leaves against γ-radiation-induced oxidative stress in rats		stress due to γ radiation, stabilize antioxidant enzymes, and repair liver, kidney, and hematopoietic tissue.	oids act as ROS scavengers.	al analysis, γ-radiation exposed rat model, biochemical tests (SOD, CAT, GPx), hematology, histopathology.	MDA, improved histological structure of organs.	single dose, not tested in vitro.	of C. cainito are relevant as antioxidants — important for proving the activity of the active metabolites of sapodilla through metabolomics + chemometrics.
Synthesis and antiparasitic activity of lupeol acetate N-alkyl-arylsulfonamide derivatives	(Li et al., 2015)	Lupeol acetate can be modified into derivatives with high antiparasitic activity and synergy with metronidazole.	Modification of triterpene structure enhances bioactivity; role of parasite cell membrane interactions.	Isolation of lupeol acetate, synthesis of chemical derivatives, in vitro antiparasitic test.	Certain derivatives are more potent than native lupeol and synergistic with metronidazole.	Focus on antiparasitics, no assessment of antioxidants, no metabolomics.	Shows that triterpene (lupeol) is an important metabolite — relevant for metabolomic studies of sapodilla.
Chrysophyllum cainito: A Tropical Fruit with Multiple Health Benefits	(Doan, 2020)	Comprehensive review of phytonutrients, antioxidants, antidiabetics, anti-inflammatory, anticancer properties of fruits & leaves.	Antioxidant mechanisms of polyphenols & flavonoids; contribution of secondary metabolites to bioactivity.	Narrative review of primary studies.	Identification of active compounds (quercetin, catechin, gallic acid, procyanidins, lupeol, β-amyrin) & biological activities.	Many in vitro studies, lack clinical data, have not used comprehensive metabolomics.	Providing a strong basis that tropical plants are rich in active metabolites — supporting the use of metabolomics for sapodilla.
Cytotoxicity of polyphenolic fraction of Chrysophyllum cainito fruit on osteosarcoma cells	(Li et al., 2015)	Fruit polyphenolic fractions increase ROS and trigger apoptosis in osteosarcoma cells..	High doses of polyphenols can be pro-oxidant in cancer cells.	Fruit extraction, ethyl acetate fractionation, DPPH, FRAP, ROS, MTT assay on cells.	Powerful antioxidant in vitro; in cancer cells produces ROS and causes cell death.	No major metabolite identification; no LC-MS; no in vivo.	Confirming the presence of important active metabolites relevant for the metabolomic profile of sapodilla.
Phytochemical characterization and antioxidant activities of C. cainito	(Yang et al., 2015)	Variation in metabolite composition between plant parts; antioxidant	Phenolics & flavonoids as the main determinants of antioxidant activity.	Extraction, TPC/TFC, LC profiling, DPPH test, ABTS, FRAP.	Significant metabolite variations in leaves, fruits, seeds; high	Not using untargeted HRMS; no chemometric integration yet.	Most relevant — your research also compared

Research titles	Author	Key Insights	Theory Used	Method	Result	Limitations	Correlation with Research
(An Acad Bras Cienc)		activity differs between organs.			antioxidant activity.		metabolites of sapodilla leaves, stems, and fruits using metabolomics + chemometrics.

However, the absence of untargeted HRMS analysis and the lack of chemometric approaches limit the study's ability to comprehensively elucidate metabolite structures and to identify relational patterns among the metabolites.

Collectively, these studies demonstrate that *Chrysophyllum cainito* possesses substantial pharmacological potential supported by its diverse array of secondary metabolites (Ningsih et al., 2020; Tapia-Álvarez et al., 2025; Wang et al., 2021). However, most existing research remains limited to basic analytical methods and does not incorporate modern analytical technologies such as high-resolution metabolomics and chemometric modeling. Therefore, further research employing these advanced approaches is essential to systematically identify key metabolites, strengthen the understanding of the underlying bioactivity mechanisms, and support the development of *C. cainito* as a promising natural source of bioactive compounds.

Conclusion

The literature indicates that *Chrysophyllum cainito* possesses strong bioactive potential, primarily through its polyphenols, flavonoids, and triterpenes such as lupeol, which contribute to its antioxidant, antiparasitic, and cytotoxic activities. However, most existing studies remain limited to basic phytochemical analyses and have not yet employed metabolomic and chemometric approaches capable of providing comprehensive metabolite mapping. Therefore, further research utilizing modern analytical techniques is needed to identify key metabolites and to strengthen the understanding of the mechanisms underlying the plant's bioactivity.

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